ARCHIVES OF PATHOLOGY

VOLUME 18 AUGUST 1934 NUMBER 2

THE RENAL GLOMERULUS IN VARIOUS FORMS OF NEPHROSIS

DWIGHT L. WILBUR, M.D.
Division of Medicine, the Mayo Clinic
ROCHESTER, MINN.

The desire to correlate anatomic with physiologic changes has been one of the driving forces in the advancement of knowledge. It has gradually led to the study of minute phenomena either through closer and more prolonged observation or through the introduction of newer methods allowing the discovery of new facts. These comments apply in particular to recent efforts which have been extended in regard to histologic changes occurring in the kidney and especially in the glomerulus in various types of renal disease. The application to the kidney of the stain combining Mallory's aniline blue and Heidenhain's azan carmine as described by McGregor [1] has opened an entirely new approach to study of the structure of the normal glomerulus, and it has brought out some important considerations, not only of glomerular structure, but also of the pathogenesis of glomerular disease. Studies have recently been published [2] regarding the glomerulus in the normal kidney of man in lipoid nephrosis, clinical glomerular nephritis, hypertension, eclampsia and subacute bacterial endocarditis. The present article will deal with my observations of the glomerulus in cases of simple nephrosis.

Nephrosis is generally considered to be a condition in which there are degenerative renal changes in contradistinction to inflammatory or nephritic and vascular or nephrosclerotic changes. Some use the term "tubular nephritis" or "parenchymatous nephritis" to designate the condition which others call "nephrosis." Cases of nephrosis are essentially in two main groups: (1) that of the so-called lipoid or chronic nephrosis and (2) that of simple nephrosis. Lipoid or chronic nephrosis is probably a distinct renal disease, often associated with chronic glomerular nephritis, and bears no evident relationship to the various types of simple nephrosis. The latter is the result of the action on the kidney of some abnormal substance producing degenerative changes of varying degree, and the name assumed for the individual type is frequently that

Work done in the Section on Pathologic Anatomy, the Mayo Clinic.

1. McGregor, Leone: Am. J. Path. **5**:545, 1929.
2. Wilbur, D. L.: Arch. Path. **12**:413, 1931.

of the supposed active agent; that is, bile nephrosis, chemical or corrosive mercuric chloride nephrosis, etc. In view of the paucity of knowledge, classifications of these conditions, whether based on etiologic, clinical or pathologic grounds, are highly controversial, probably inaccurate and subject to revision. However, for purposes of study it is helpful temporarily to classify these cases according to types. In the present study, the following types have been recognized: (1) acute simple or toxic nephrosis; (2) bile nephrosis; (3) chemical nephrosis; (4) renal changes of pregnancy and eclampsia.

Studies of the glomerulus in cases of lipoid nephrosis will be considered separately.

Before the observations are considered in detail, attention should be directed to several facts. In the first place, there may be considerable debate as to the primary or secondary nature of the renal lesion in cases of simple nephrosis. This question is of great importance. In the second place, it should be recalled that the glomerulus is but one part of the anatomic and functional unit of the kidney. Although for purposes of anatomic and physiologic study it is profitable to consider the glomerulus separately because of its different structure and function, care must be exercised in drawing too many sweeping conclusions from the study of a part of the unit only. Last, it should be pointed out that visible anatomic and physiologic changes may not always coincide and that therefore an organ which appears normal anatomically may have been functioning abnormally, and vice versa.

MATERIAL FOR STUDY

The selection of the cases for this study of glomerular characteristics in nephrosis requires some explanation. It was possible to obtain cases by two methods. First, the selection could be made on the basis of clinical data and diagnosis only; second, it could be made on the basis of the pathologic diagnosis. The latter method of choosing cases was followed because it seemed more likely to include the type of cases wanted, particularly since the pathologic diagnoses were made with knowledge of the clinical findings. Consequently the records of the Section on Pathologic Anatomy of the Mayo Clinic from 1923 to 1931 inclusive were searched, and all cases in which a diagnosis of nephrosis or its approximate equivalent had been made were included in the study. The majority of the cases may be considered as examples of acute simple or toxic nephrosis or of terminal nephrosis. Many of them occurred in patients who had been operated on and in whom, postoperatively, such complications as infections and gastro-intestinal obstruction or retention developed.

The following modified method [3] of using the Mallory-Heidenhain stain proved very satisfactory for routine work.

Take tissues fixed in formaldehyde solution (if the tissue is old, use the ammonia bath for one hour). Make paraffin sections 4 or 5 microns thick. Dry the sections in the oven at 37 C. over night. Remove the paraffin from the sections and wash them in water; then put them in Zenker's solution for one hour. Wash them in tap water for ten minutes, remove the crystals with compound solution of iodine and clear the sections in 2 per cent sodium hyposulphate and water.

1. Place the sections for four hours in a first Weigert mordant made as follows: potassium bichromate, 5 Gm.; fluorochrome, 2 Gm., and distilled water, 100 cc., boiled together.

2. Wash the sections in tap water and place for two hours in a second Weigert mordant made as follows: acetate of copper, 5 Gm.; fluorochrome, 2 Gm., and distilled water, 100 cc., boiled together.

3. When the mixture is cold, acetic acid (36 per cent), 5 cc., and diluted formaldehyde solution, 10 cc., are added.

If the tissue is old, replace the sections in the ammonia bath for two minutes. Wash for one hour in running tap water.

4. Place for forty minutes in azan carmine, prepared as follows: Put 1 Gm. of azan carmine in 100 cc. of distilled water, heat, cool, filter at room temperature and add 1 cc. of glacial acetic acid.

5. Differentiate in aniline alcohol (watch under the microscope). For aniline alcohol add 1 cc. of aniline oil to 100 cc. of 95 per cent alcohol.

6. Remove aniline with acid alcohol and wash in water quickly.

7. Place for two hours in 5 per cent phosphotungstic acid. Wash quickly in water.

8. Place for from ten to twenty minutes in Mallory's aniline blue and orange G without fuchsin. This is made by mixing together aniline blue, 0.5 Gm.; orange G, 2 Gm., and distilled water, 100 cc., and then adding acetic acid.

9. Wash quickly in water and differentiate in absolute alcohol (watch under the microscope).

10. Treat with xylene and balsam and mount.

Studies of the normal renal glomerulus by this method have already been published and serve as a basis for the present observations.

I. ACUTE SIMPLE NEPHROSIS

Acute simple nephrosis, a type of that group 2, previously defined, which is designated by the term simple nephrosis, comprises the majority of cases of the so-called nephroses. Acute simple nephrosis is known also as toxic nephrosis, terminal nephrosis, cloudy swelling, acute tubular nephritis, acute parenchymatous nephritis and so forth. A strict limitation of this type is naturally impossible, for it depends on whether one is speaking in terms of pathologic changes or in terms of clinical obser-

3. de Galantha, Elena: Personal communication to the author.

vations. One can define it perhaps as a disturbance, usually of short duration, with primarily degenerative changes in the renal tissue, principally the tubules, manifested clinically by albuminuria and occasionally by cylindruria, the result of a state of fever or so-called toxemia. It should be emphasized that the renal disease is generally but one expression of a widespread so-called toxic effect, and that other organs may be and usually are likewise affected. Consequently, the renal changes are secondary, and the disease in the kidney is not primarily a renal disease, such as is suggested in a case of chronic glomerular nephritis. Another point to be stressed is that so far as the lesion in the kidney is concerned it is not necessarily irreversible and consequently it is one from which clinical recovery can occur. This fact in itself distinguishes acute simple nephrosis from acute nephritis in a certain proportion of cases, the latter disease not infrequently assuming a chronic course. The limits of acute simple nephrosis are widely apart. On the one hand is a mild degree of renal degenerative change accompanying a febrile disease and demonstrable clinically perhaps by albuminuria only; on the other hand, a disease very severe and associated with marked renal changes which may in part be responsible for the death of the patient. The latter changes are unusual under ordinary conditions of febrile or so-called toxic states, although known to accompany virulent infections and to follow the use of certain drugs.

It is to be expected that since acute simple nephrosis is generally a disturbance of short duration and frequently a terminal phenomenon of infectious and postoperative states it should occur in the presence of such long-standing renal conditions as arteriosclerotic renal disease, mild grades of hydronephrosis and local infections such as pyelitis. It seems reasonable to suppose not only that the nephrotic element of the picture is quite independent of, and therefore largely coincidental with, such other lesions, but that it is, in addition, not necessarily predisposed to by the preexisting disease. It is possible that with associated pyelitis, which is an inflammatory condition, a renal lesion should not be classified as nephrosis.

The occurrence of cases in which there is a combination of lesions must be recognized in order to avoid confusion concerning the etiologic interpretation of renal, and especially glomerular, changes. Since arteriosclerosis in particular is frequently associated with glomerular changes it must be distinctly recalled that in an arteriosclerotic kidney which is also the seat of nephrotic change the glomerular changes may more likely be due to the vascular than to the nephrotic condition. On the whole, the changes observed in cases in which there were combined lesions were not distinctive, and no unusual features seem to have been produced by a combination of diseases.

In addition, the changes in nephrosis are usually of short duration, since the disease processes from which nephrosis results are usually of short duration, leading either to death or to complete recovery. Consequently, acute nephrosis as a rule is not the "going concern" that chronic nephritis is, which, once on its course, usually goes to its completion.

The renal changes in acute simple nephrosis are generally described as follows: The kidneys are usually enlarged, smooth and pale or indistinct in color. The organs may appear boiled or yellowish. The edges of cut sections often become everted, and the sections are frequently opaque and present indistinct cortical markings. The surface may appear fatty. On microscopic study the glomeruli are usually reported to be normal, and in the tubules there usually are any number of changes from cloudy swelling and fatty degeneration to necrosis. Formation of casts is frequent. Finer studies of the glomeruli reveal occasionally: (1) swelling or various forms of degeneration of the epithelial cells of the tuft, the degree of degeneration frequently being similar to that present in the associated tubules; (2) desquamation of the epithelial cells of the tuft; (3) granules of albuminous material in the capsular spaces, variable in amount and occasionally appearing like hyalin; (4) more rarely, some swelling of the endothelial cells of the tuft or slight swelling of the basement membrane, and (5) collections of variable numbers of polymorphonuclear and mononuclear cells in the capillaries. Necrosis of the tufts has been reported but is very rarely seen under these conditions. Edema of the interstitial tissue may also be observed.

The present study deals with forty-one cases. In the majority of these cases the renal changes developed subsequent to operations on organs other than the kidneys. In other instances severe infections, such as septicemia, led to a fatal termination. In numerous instances obstruction of the gastro-intestinal tract was present.

The majority of the kidneys were grossly similar to those noted previously; that is, they were enlarged smooth kidneys, pale or indistinct in color, often appearing boiled or yellowish, and the cut sections presented opaque and frequently indistinct cortical markings, with edges that became everted. In those kidneys in which there was associated arteriosclerotic change or hydronephrosis the findings characteristic of these lesions were generally present also.

In the consideration of the microscopic observations of the glomeruli it was almost impossible to segregate them satisfactorily; consequently a more or less arbitrary gathering into divisions and subdivisions has been resorted to (table 1).

Division 1. Cases in Which There Were Distinct Glomerular Changes.—Ten cases fell into this division. In the majority (six cases) the changes could be ascribed to associated hypertensive or arteriosclerotic

change in the kidneys. In the minority (four cases) the explanation of the glomerular changes was less definite. In one of the four cases the patient was aged 59 years, and the renal changes may have been early senile changes. In another instance the kidneys were those of a boy of 13 years who succumbed to a very virulent infection, and the changes, as well as the clinical findings, were more suggestive of acute glomerular nephritis. In the remaining two cases the glomerular changes could not definitely be ascribed to any particular process.

TABLE 1.—*Arbitrary Division, for Purposes of Study Only, of the Forty-One Cases of Acute Simple Nephrosis*

Division 1	Division 2	
	Cases in which glomerular changes were not distinct (31 cases)	
Cases in which glomerular changes were distinct (10 cases)	Subdivision 1 Cases in which a clinical diagnosis of renal disease, insufficiency or uremia had been made (11 cases)	Subdivision 2 Cases in which a clinical diagnosis of renal disease, insufficiency or uremia had had not been made (20 cases)

Division 2. Cases in Which There Were No Distinct Glomerular Lesions.—Thirty-one cases fell into this division. For purposes of study they were divided into two subdivisions composed, respectively, of eleven cases in which a clinical diagnosis of associated renal disease, insufficiency or uremia had been made and twenty cases in which such a diagnosis had not been made. It was thought that such subdivision might lead to observations that would in turn elucidate the problem of the correlation of anatomic and physiologic disturbances, for in kidneys from patients who gave clinical evidence of renal disease such observations would be of distinct value. In these cases microscopic study showed the glomeruli to be essentially normal. The majority of them presented normal amounts of blood within the capillary loops and tufts of approximately normal size.

However, in many of the glomeruli minor changes were to be noted. They are considered minor from the anatomic point of view, although from the physiologic point of view it is conceivable that they may have been of great significance. These changes included: (1) granular débris, generally considered to be disintegrated cytoplasm or possibly coagulated albumin; (2) swelling, degeneration and desquamation of the epithelial cells of the tufts; (3) occasionally irregular thickening of the glomerular basement membrane, and (4) swelling or at times even slight increase in the number of the endothelial cells within the tufts. Such changes can readily be ascribed to degenerative processes and are not infrequently seen in the kidneys of patients who have died of acute infections, most of whose parenchymatous organs are affected by cloudy swelling.

The tubular changes were chiefly cloudy swelling and degeneration of the cells, producing partial obstruction of the tubular lumens; frequently there was dilatation of the tubules, at times very marked and associated with narrowing of the cell layer, together with degeneration of various types and extent. Granular débris in the tubular lumens was present in every case, whereas hyaline casts were less frequently noted. In addition to the usual changes noted in these kidneys, in three cases there was evidence of marked interstitial edema that not only separated the tubules from each other but also separated the intertubular capillaries from the tubules.

Another type of acute simple nephrosis is that encountered in cases of hyperemesis gravidarum. A consideration of the changes observed in such cases has been made so recently by Bell [4] that detailed consideration of the changes will not be made in this paper. The essential change is tubular degeneration. The glomeruli generally appear normal.

Contrast Between the Two Subdivisions of Cases of Division 2.—The clinical findings in the eleven cases included in the first subdivision were definite. The clinical diagnosis of renal disease, insufficiency or uremia was made because of elevated values of blood urea, significant urinary findings and occasionally edema, hypertension and oliguria. In every instance except one, abnormal urine was noted during the course of the disease; there were relatively large amounts of albumin, numerous casts and occasional erythrocytes and pus cells in the urinary sediment. In three instances sugar was also present in the urine, but this may perhaps be accounted for by the fact that solutions of dextrose had been administered intravenously. In many instances the specific gravity of the urine was 1.020 or more, and the urinary output in many of them, fair or good (from 500 to 1,000 cc. daily). Urine with this degree of specific gravity and in this daily volume is not generally found in ordinary cases of renal insufficiency, regardless of the cause. It must be noted that the relatively high specific gravity in some of these cases may have been due to the large amounts of albumin in the urine. Edema was absent in all except two of the cases. A study of the values of the blood urea in all cases except one was made, and in each instance the value of the urea was definitely above the normal; the highest value recorded was 388 mg. in 100 cc. of blood. It is interesting that in one case nephrectomy had been done several years previously for an independent condition.

In the second subdivision (twenty cases), which included those cases without clinical evidence of renal disease, the following features were noted: Studies of the urine on the days preceding death revealed a good output in ten cases, a fair output in seven cases, a poor output in one case,

4. Bell, E. T.: Am. J. Path. **8**:1, 1932.

and no data in two cases on the days preceding death. In other words, oliguria was not a distinctive feature. In only four of the cases were the urinary findings distinctly abnormal; in seven cases there were slight abnormalities, such as a small amount of albumin or a few casts; in three cases the urine was normal, and in six cases the condition of the urine was not noted. The specific gravity of the urine in nine cases was 1.020 or higher, and was recorded as less than 1.015 in only three cases. Estimates of blood urea were made in ten cases; in seven of these the value was elevated terminally, but in one case only was the value more than 100 mg. in 100 cc. of blood.

From the clinical standpoint, therefore, the difference between the two groups was one of degree only, for qualitatively the changes were similar.

Pathologically, in contrasting kidneys of these two subdivisions, several variations were noted. The differences were not qualitative but quantitative and, as is to be expected, in the first subdivision (cases in which clinical diagnoses of renal disease, insufficiency or uremia had been made) the findings clinically and anatomically were more prominent than in the second subdivision, cases in which clinical diagnoses had not been made. The renal changes noted in this subdivision consisted essentially in the greater prominence of the minor changes already noted as being found in the glomeruli in cases of these two subdivisions. The more outstanding renal changes were, most likely, dependent on the more profound "toxemia" which had resulted from the serious disease that secondarily had led to renal injury.

Case 1.—No one of the cases can be considered typical of the entire group of cases of acute simple nephrosis. However, one of them is of such interest from the standpoint of demonstrating the failure of correlation between clinical and pathologic features in these cases that it will be reported in detail.

A woman, 45 years of age, came to the clinic July 5, 1928, because of loss of vision. The past medical history was essentially negative save that she had had numerous acute infectious diseases. The menopause had occurred at the age of 27 years, without apparent cause, and since that time there had been a gain of 75 pounds (34 Kg.). Approximately a year and a half before her visit dimness of vision gradually developed, and was more marked in the left eye than in the right.

Physical examination gave essentially negative results. The woman was obese, however. Blood pressure on two occasions was respectively 110 and 135 mm. of mercury, systolic, and 88 and 85 mm. diastolic. The urine had a specific gravity of 1.024 and 1.028, was acid in reaction, and contained albumin graded 3 and 4, an occasional hyaline cast and many granular casts. The return of phenolsulphonphthalein was 50 per cent in two hours. The value of the blood urea was 26 mg. in 100 cc. of whole blood, the value of protein in 100 cc. of serum was 6.1 Gm., and the fats totaled 525 mg. in 100 cc. of blood. The basal metabolic rate was —3.

A roentgenogram of the skull disclosed that the sella turcica was markedly enlarged, and that the clinoid processes were completely flattened. Ophthalmologic studies revealed a visual defect in each temporal quadrant.

There was no history of previous renal disease. In view of the absence of evidence of renal insufficiency and the good general condition of the patient, aspiration of a pituitary cyst was carried out July 18. The tumor proved to be adenocarcinoma, graded 2.

The postoperative condition was satisfactory for twenty-four hours, after which the blood pressure began to rise and reached a peak of 190 mm., systolic, and

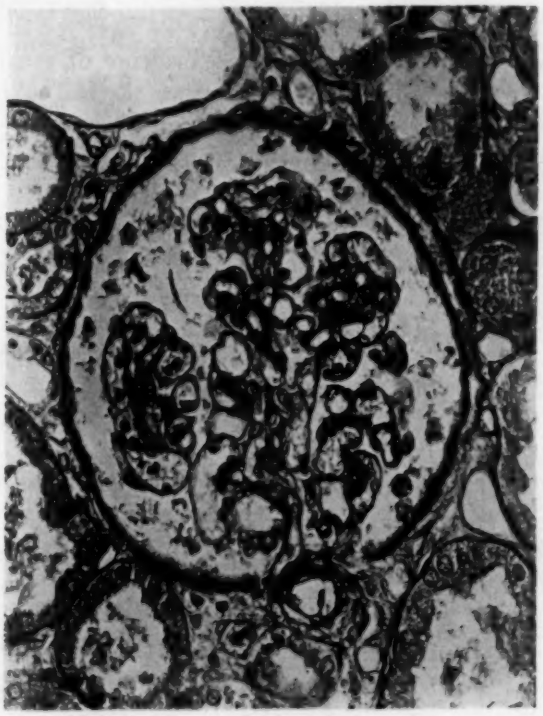


Fig. 1 (case 1).—Renal glomerulus from a patient with essential hypertension and simple nephrosis as a terminal event. The basement membrane of the tuft is thickened, particularly in the left half of the photomicrograph (× 350).

92 mm., diastolic, following which it steadily dropped during the twelve hours preceding death. The urinary output gradually decreased; the day following operation it was 100 cc., and the following day, 200 cc. Urinalysis disclosed albumin graded 4, a few hyaline casts, and occasional erythrocytes in the urinary residuum. The value of the blood urea rose to 139 mg. in 100 cc. The intake of fluid during the forty-eight hours between the operation and the time of death was 4,200 cc. Visible edema did not occur. Death occurred July 21.

The primary and secondary causes of death were recorded as carcinoma of the pituitary body and chronic diffuse nephritis (nephrosis). The right kidney weighed 169 Gm., and the left, 160 Gm. The capsules stripped with slight diffi-

culty, leaving smooth, purplish-red surfaces which were opaque in appearance. The glomeruli appeared normal in size and number, and presented the usual number of erythrocytes. There was considerable débris in the capsular spaces. The epithelial cells of the tufts were possibly slightly increased in number. Many of them were large and swollen. The endothelial cells appeared to be normal. The glomerular basement membrane appeared normal, although it presented occasional areas of thickening in the hilar regions of the tufts. The blood vessels and interstitial tissue appeared normal, while the tubules disclosed some dilatation and degeneration, with areas of thinning of the cellular cytoplasm. These changes were marked in some areas; elsewhere, the tubules appeared normal, although they contained much granular débris and some hyaline casts (fig. 1).

This case is interesting. The clinical evidence of renal disease was limited to the urinary findings, which were marked and consistently found. There was no evidence of edema or of lowering of the value of the serum protein, so characteristic of lipoid nephrosis. The normal appearance of the glomeruli was surprising in view of the marked urinary changes, and is illustrative of the fact that albuminuria may occur in the absence of apparent anatomic glomerular changes.

COMMENT

Several interesting problems are raised in a consideration of the pathogenesis of the symptoms in cases of acute simple nephrosis. The renal lesions are generally considered to be secondary to a primary disease, to arise as a result of so-called toxemia, and to be degenerative. As one might expect, the most highly differentiated tissue in the kidney, that is, the cells of the tubules, is the one most markedly affected. However, the glomeruli may participate to the extent of demonstrating mild degenerative changes, often proportional to the severity of the primary process. Consideration of all of the many clinical features observed in cases of acute simple nephrosis is beyond the scope of this presentation. However, it will be of interest to consider certain features which have a significant bearing on the subject.

The changes in the urine are those which would be anticipated: albuminuria, cylindruria and the occasional presence of erythrocytes and leukocytes in the sediment. From causes which are frequently, in part, extrarenal the urinary volume may be low, and marked oliguria is not infrequent. This process has been called the result of prerenal deviation of fluid or the retention of water by the tissues, so that a sufficient amount is not present for adequate formation of urine.

In considering some of the clinical features of cases of nephrosis, especially those associated with intestinal obstruction and conditions of dehydration, much discussion has been given to the mechanisms resulting in alterations in the chemical constituents of the blood, with particular reference to elevation of its nitrogenous content. Since the renal changes in these conditions are secondary to disease elsewhere it frequently has

been pointed out that the chemical changes which occur in the urine, and particularly in the blood, are not of necessity due to, or explained by, the renal changes only. Controversy has arisen, therefore, as to whether or not the elevation of the values of the blood urea in some of these cases is the result of renal or of so-called extrarenal factors, or of a combination of the two. Included in the extrarenal factors may be such mechanisms as dehydration, increased production of urea resulting from increased destruction of protein, and such alterations in the chemistry of the body as lead to retention of urea for preservation of osmotic relationships and so forth. The part played by the injured kidney cannot always be estimated. As Peters and Van Slyke [5] stated: "That the efficiency of the kidney is diminished cannot be denied. That it is the chief cause of the azotemia is open to question." If renal injury is a factor in the elevation of the value of the blood urea in some of these cases, evidence as yet is not available to determine whether or not the renal mechanism retaining the urea is similar to that in cases of glomerular nephritis with uremia.

In the opinion of some investigators the principal cause of the symptoms of renal insufficiency in these cases is the oliguria with the result that insufficient quantities of urine are formed to allow excretion of the necessary waste products in adequate amounts. However, as indicated in some of the cases in the present series in which the volume of urine seemed adequate and the urine of relatively high specific gravity, this explanation apparently does not suit all cases.

Further evidence that will help to settle some of these problems must come from accurate studies made clinically during the course of acute simple nephrosis of the type described, with evaluation of the metabolism of water, urea, minerals and other waste products.

In many of these cases, gastro-intestinal retention was present secondary to duodenal and pyloric obstruction, and in other cases, it was secondary to peritonitis and intestinal obstruction. As pointed out by Brown, Eusterman, Hartman and Rowntree,[6] such conditions are frequently associated with "toxic nephritis," a syndrome presenting characteristic chemical changes in the blood and urine, and presenting at postmortem examination renal lesions characterized by tubular epithelial degeneration of a fatty and granular nature, occasionally with deposits of calcium, and without marked changes in the glomeruli. Zeman, Friedman and Mann [7] studied similar cases and characterized the renal

5. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1931, vol. 1, p. 298.

6. Brown, G. E.; Eusterman, G. B.; Hartman, H. R., and Rowntree, L. G.: Arch. Int. Med. **32**:425, 1923.

7. Zeman, F. D.; Friedman, William, and Mann, L. T.: Proc. New York Path. Soc. **24**:41, 1924.

lesions as entirely degenerative. They expressed the belief that the deposition of calcium in the cells of the tubules is not secondary to the administration of calcium salts. Changes similar to these have been found in many of the kidneys studied in this series. The absence of distinctive glomerular changes is confirmed in the majority of these cases, although elevation of the value of the blood urea was a prominent feature in many of them.

II. BILE NEPHROSIS

In the presence of obstructive jaundice the kidneys as well as other organs are bile-stained. With the staining there occur toxic effects which are known as bile poisoning, bile toxemia and so forth. The mechanism producing this change has never been fully understood, nor has it been expressed better than by the vague term "toxemia" or "toxic effect"; nevertheless, considerable clinical interest and importance are attached to the effect produced by obstructive jaundice on organs other than the liver. The internist has appreciated the fact that relief of obstructive jaundice must not be too long delayed, because of its damaging effect on the liver and other organs, and the surgeon has discovered that the three great dangers in surgical treatment of obstructive jaundice are hemorrhage, renal insufficiency, uremia and hepatic insufficiency. Renal insufficiency may be precipitated in cases of obstructive jaundice by the shock incident to surgical operation or anesthesia.

Considerable speculation has arisen concerning the active agent that produces renal injury and insufficiency in cases of obstructive jaundice. As possible agents, bile salts, bile pigments, associated infections and vasopressor and depressor or other toxic substances liberated from the liver have been suggested.

Clinical, and particularly experimental, evidence has been presented to prove or to disprove the importance of these various factors in the secondary effects of obstructive jaundice. As evidence accumulates it seems to point more and more to the importance of certain toxic or pressor substances elaborated by the hepatic tissue, or perhaps resulting from destruction of the hepatic cells, rather than to bile salts, bile pigments or infections.

Evidence of an adverse effect on the kidney in cases of jaundice is demonstrated clinically by the occurrence of abnormal substances in the urine, the result of "renal irritation." This may be mild or severe, more likely the former. Apparently in the early stages of jaundice renal injury may be more marked, since albuminuria is then more prominent than it is subsequently if jaundice continues for some time. Fitz-Hugh [8] pointed out that in twenty-five consecutive cases of catarrhal jaundice in persons who were, for the most part, healthy young adults,

8. Fitz-Hugh, Thomas, Jr.: M. Clin. North America **12**:1101, 1929.

twelve of the patients had a cloud of albumin in the urine, eleven had a faint to heavy trace, and only two had less than a faint trace during the early stages of the jaundice. Similar observations have often been made in cases of obstructive jaundice. Still more remarkable evidence of the relationship of hepatic and renal disease is presented in a case reported by Helwig and Orr,[9] in which traumatic pulpefaction of the liver without rupture and with extreme jaundice and diffuse hemorrhages into serous cavities led to oliguria, elevated values of the nitrogen and creatinine of the blood and extensive histologic changes in the renal tubules. A similar case had been reported by Furtwaengler[10] in 1927. In the case reported by Helwig and Orr, erythrocytes and albumin were found continuously in the urine during the six days of the illness, and suppression of the urine was present to the extent that not more than 200 cc. of urine was passed during any one day. In addition, the blood pressure rose to 150 mm. of mercury, systolic, and 80, diastolic. Generalized edema developed, and jaundice occurred on the second day after the accident. The level of the nonprotein nitrogen rose steadily from 75 to 250 mg. and that of creatinine from 3.7 to 25 mg. in 100 cc. of blood. The kidneys were very large, swollen and soft and together weighed 580 Gm. Microscopically, they presented marked degeneration and even necrosis of some of the tubular cells, chiefly those of the convoluted tubules. The epithelium of the more highly differentiated cells was generally pigmented with a fine dust of greenish granules. The glomeruli presented swelling of the epithelium lining Bowman's capsule, and in the space between the tuft and the capsule erythrocytes were scattered about. In the capillary loops the endothelium was somewhat swollen, and in the tortuous capillary channels a few polymorphonuclear leukocytes were seen here and there. Stains for fat revealed no evidence of fatty degeneration or embolism in the kidneys.

This report is given in detail because it presents in a very striking way the results of an "acute experiment" illustrating the profound effect of hepatic necrosis and jaundice on the kidney. Although, in view of the extensive hepatic injury, the whole picture may not properly be said to be due to the jaundice alone, nevertheless there is a similarity in this case to cases of marked and prolonged obstructive jaundice in that in such cases extensive and irreparable hepatic injury occurs also.

An apparent adverse effect on the liver of disease of the renal and urinary tracts has been described by Dourmashkin[11] and by Fitz-Hugh. They reported cases of cholemia apparently induced by and "following instrumentation of patients having obstructive lesions of the urinary

9. Helwig, F. C., and Orr, T. G.: Arch. Surg. **24**:136, 1932.
10. Furtwaengler, A., quoted by Helwig and Orr.[9]
11. Dourmashkin, R. L.: J. A. M. A. **90**:908, 1928.

tract with coexisting hepatic cirrhosis." It is suggested that infection may play a significant part in this unusual clinical picture. Further evidence of the relationship of hepatic and renal disease has been presented recently by Helwig and Schutz,[12] who reported clinical and experimental observations on a hepatic-renal syndrome which they considered distinct from bile nephrosis. They expressed the belief that the syndrome was due to a potent toxin produced from injured hepatic tissue acting more or less specifically on the kidneys.

The changes in the kidney occurring in cases of cholemic nephrosis were described by Fahr [13] as follows: The kidneys are slightly enlarged and are irregularly or uniformly stained with bile. Microscopically, in Bowman's capsule are bile-stained rounded or granular masses of albumin. The capsular spaces may contain granules of bilirubin pigment or numerous desquamated epithelial cells or fragments, and occasionally the glomeruli reveal fine fat droplets. Similar bile-stained albuminous masses occur in the tubular lumens, and they may be so numerous as to form casts. Dilatation of the tubules, with flattening of the epithelium, may be present in such areas of cast formation. The epithelial cells may be stuffed with bile pigments and may show simple albuminous or vacuolar degeneration, occasionally necrosis. Exudative phenomena are absent. Kaufman [14] reported that the tubular epithelium undergoes fatty degeneration or necrosis and exfoliation, an injury caused by bile acids. Quincke [15] noted that the glomeruli remain practically unstained by bile.

The present study includes thirteen cases in which a diagnosis of bile nephrosis or its equivalent was made at necropsy. The methods of study and preparation of tissue were the same as those recorded previously.[2] Obstructive jaundice was present in each case, and the clinical data suggest a rather uniform sampling of the types of cases in which obstructive jaundice is present ordinarily seen clinically. The jaundice lasted from two days to two years and was constant or intermittent and of varied depth. Most of the patients were more than 45 years of age, as obstructive jaundice is rarely fatal before this age. In no instance was there any history of renal disease prior to the onset of the jaundice, and in some instances studies failed to reveal evidence of renal disease before the patients came to operation. In a few cases moderate hypertension had been present. The findings referable to the

12. Helwig, F. C., and Schutz, C. B.: Surg., Gynec. & Obst. **55**:570, 1932.

13. Fahr, T., in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1925, vol. 6, pt. 1.

14. Kaufman, Eduard: Pathology for Students and Practitioners, Philadelphia, P. Blakiston's Sons & Company, 1929, vol. 2.

15. Quincke, H., in Nothnagel, H.: Spezielle Pathologie und Therapie, Vienna, Alfred Hölder, 1899, vol. 18, p. 63.

urinary tract consisted chiefly of albuminuria, occasional formation of casts, and occasional erythrocytes and leukocytes in the urinary sediment. In some of the surgical cases evidence of increased concentration of urea in the blood developed after operation, and in nine of the thirteen cases the value of the blood urea was elevated prior to the death of the patients. In three cases gastric retention and vomiting may have been a significant factor in producing the elevation of the blood urea. In the three cases in which it was noted the value of the blood chloride shortly before death was within normal limits. In the majority of the cases the records show that a fairly satisfactory urinary output was maintained, and even in some of the cases with elevated levels of blood urea, oliguria was not a feature. Renal insufficiency or uremia was given as a primary or a secondary cause of death in four of the thirteen cases. Most of the patients died from six to twelve days after operation. This includes four cases in which "renal insufficiency" was considered a factor.

Pathologic data show that in only two cases in the group were the kidneys of normal weight. In the remainder the kidneys were enlarged, the largest kidneys in the series weighing together 549 Gm. The majority of the kidneys were smooth, bile-stained and soft or flabby. In the majority of cases the glomeruli appeared normal microscopically. In almost all cases the glomerular epithelium appeared normal, although in a few there was some swelling or increase in the size of the epithelial cells of the tuft with at times excessive desquamation. In only six of the thirteen cases was there evidence of increase in the number of endothelial cells, and in the majority of these cases the increase was slight and associated with some swelling of the cells. The glomerular membrane appeared normal in most of the sections, although in some the membrane was irregularly thickened, particularly in the central or hilar portions, a finding probably associated with age. The occurrence of granular débris, probably disintegrated cellular cytoplasm, in the capsule of Bowman was not infrequent.

Tubular changes consisted chiefly of dilatation of the convoluted tubules with narrowing and degeneration of the epithelial cells, occasionally swelling with partial obstruction of the tubules, considerable granular débris and occasional casts within the tubular lumens, as well as bile pigment in variable amounts either within the cells or in the tubular or intertubular spaces. Changes in the interstitial tissue were slight and consisted of occasional patches of fibrous thickening or localized areas of edema; abnormal collections of cells were absent. In the kidneys of the older patients in the group sclerotic patches with hyalinized glomeruli and atrophic tubules were not uncommon. In figure 2 may be noted a renal glomerulus from a patient with bile nephrosis.

Case 2.—A man, aged 43 years, came to the Mayo Clinic on Sept. 24, 1927, because of attacks of colic in the right upper quadrant of the abdomen of four years' duration and jaundice of three weeks' duration. The attacks of colic were characteristic of gallstone disease.

Physical examination gave essentially negative results, with exception of jaundice and obesity. The blood pressure in millimeters of mercury was 134 systolic and 94 diastolic. Urinalysis on two occasions gave negative results; the specific gravity was 1.018 and 1.020. Erythrocytes numbered 4,040,000 per cubic millimeter of blood. The value for bilirubin was 20.2 mg. in 100 cc. of serum.

On October 1, cholecystectomy and choledocholithotomy for subacute cholecystitis of grade 4, with cholelithiasis and choledocholithiasis, were performed. The postoperative course was stormy. Three days after operation the value of the urea was 143 mg. in 100 cc. of whole blood. It subsequently rose to 268 mg. and dropped

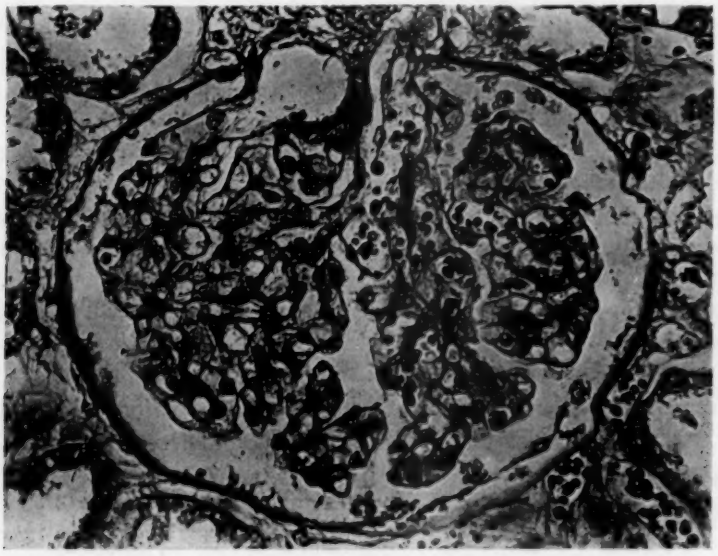


Fig. 2.—Bile nephrosis: normal glomerulus; coagulated plasma in many of the loops (× 325).

on the day of death to 250 mg. At the same time the value of the creatinine was 8 mg. in 100 cc. of whole blood, and that of the chlorides was 590 mg. in 100 cc. of plasma. Urinalysis revealed albumin graded 1+, a moderate number of hyaline casts and occasional erythrocytes and pus cells; the specific gravity was not recorded. The urinary output remained adequate, 2,645, 2,200 and 1,775 cc. on the three days preceding death. Edema did not develop. The blood pressure had not been recorded before operation. The cause of death was recorded clinically as obstructive jaundice and bronchopneumonia.

At necropsy, the right kidney weighed 250 Gm., and the left, 230 Gm. They were soft, flabby, swollen, smooth and brown. The glomeruli appeared normal. They were of the solid type. The epithelial and endothelial cells of the tufts appeared to be essentially normal, as did the basement membrane, with the exception of slight patchy thickening. The tubules were markedly dilated, and the cells revealed swelling and degeneration and contained bile pigment. The vascular walls were slightly thickened.

In this case, in which there was no evidence of preexisting renal disease, but in which jaundice was marked, evidence of renal insufficiency and injury developed after operation despite an apparently adequate output of urine. At necropsy, the kidneys presented, grossly and microscopically, the changes characteristic of bile nephrosis.

The changes noted in these kidneys may probably be considered largely degenerative and secondary to some toxic substance or substances associated with obstructive jaundice. With the exception of those cases in which previous hypertension was associated or occurred in older persons, the glomeruli in the majority of the kidneys in this series appeared essentially normal anatomically. The apparent slight increase in the endothelial cells in some of the tufts is difficult to explain and perhaps is not significant. It was not accompanied in every case by evidence of an infectious process elsewhere in the body. Clinical evidences of glomerular nephritis were lacking. Bile nephrosis is generally considered to be a degenerative disease, and glomerular lesions are considered to be absent in such cases. That glomerular injury had not occurred in a given case could not be definitely disproved. However, the presence of albumin in the urine and the occurrence of granular, probably albuminous material in the capsular spaces are very suggestive that such injury had occurred, and these findings were present in the majority of cases. The possibility that the albumin so excreted was abnormal, that is, not normal blood protein, is to be considered, since Andrews [16] and his associates suggested that the albumin in the urine in cases of nephritis may be abnormal, perhaps of hepatic origin. It is reasonable to assume that if abnormal protein exists in the blood plasma and the glomeruli are normal it will be excreted. Hayman and Bender [17] recently reported observations on the intravenous injection of plasma from three patients with nephritis who were excreting large amounts of protein. In no case did this cause albuminuria in healthy recipients.

The mechanism which produces increase of urea in the blood is not well understood. It is generally considered to be the result of either renal or extrarenal abnormalities. In cases of renal disease, the increased concentration of urea in the blood is generally associated with severe glomerular injury and disease, as is seen in cases of nephritis and nephrosclerosis, in which there is failure of excretion of urea in adequate amounts. In cases in which there is increased concentration of urea resulting from so-called extrarenal factors, the mechanism of the retention is uncertain. Many hypotheses have been advanced, but as yet none is entirely satisfactory. It is suggested by some investigators

16. Andrews, E., and Thomas, W. A.: J. A. M. A. **90**:539, 1928.
17. Hayman, J. M., Jr., and Bender, J. A.: Arch. Int. Med. **51**:447, 1933.

that elevation of the value of the blood urea due to extrarenal factors is a compensatory mechanism to maintain the osmotic pressure of the serum at normal levels in the presence of lowered values of the blood chlorides. In the three cases in the present series in which the values of the blood chlorides were determined shortly before death, those values were within normal limits. From the standpoint of the cases studied in the present series, it seems reasonable to believe that the increase in the urea in the blood in some of the cases of bile nephrosis in which it occurred was due, in part at least, to so-called extrarenal causes. The lack of microscopically apparent glomerular alterations is of significance in this connection, as is the fact that lesions of somewhat similar type, but more marked, may be found in the tubules in cases in which elevation of the blood urea is not shown. In the present series, significant anatomic differences between the cases with and those without increase in the blood urea were not noted.

As has been mentioned, the exact etiologic relationship between the obstructive jaundice and the renal lesion is not clear. Evidence points more and more to the importance of a nephrotoxic substance produced as a result of hepatic injury. The significance of the products of bile retention is uncertain since severe renal injury may occur in the presence of hepatic disease independent of jaundice, as was shown clinically and experimentally by Helwig and Schutz, but the lesions produced in the cases they described they considered were not strictly comparable to those of bile nephrosis. Interestingly enough, glomerular lesions of note were not reported in their studies.

It should be pointed out that by no means all patients with bile nephrosis succumb; as a matter of fact, the majority of patients who show this clinical change recover promptly and completely. The occurrence of a condition associated with increased concentration of urea in the blood may be a very significant contributing factor in bringing an illness to a fatal termination. There is no evidence, however, that the lesion produced in the kidney is irreparable.

III. CHEMICAL NEPHROSIS

Chemical substances which are poisonous produce varying effects on the kidneys, depending particularly on the nature and the concentration of the poison. Since the proximal convoluted tubules are the most highly specialized cells in the kidney, they are generally the most readily and most markedly affected. In addition, they come in contact with such substances in relatively high concentration because their functions result in concentration of the material in the tubular lumens. It is interesting to note that certain chemical poisons have a selective action and consequently in moderate doses may affect only a localized portion in

the renal functional unit. Suzuki [18] showed, for example, that chromium harms chiefly the first portion of the proximal convoluted tubules in the experimental animal, uranium the third portion, and mercuric chloride and cantharidin the terminal, transitional piece. If the dose is sufficiently small, these regions only will be involved, but if larger doses are given, more of each tubule becomes affected and even the glomerulus may be diseased. Although the majority of such toxic substances affect principally the tubules for reasons already mentioned, certain poisons such as crotalin (rattlesnake venom) produce profound glomerular lesions. Pearce [19] showed this glomerular lesion in the kidney of the rabbit to be an acute exudative one. It does not lead, however, to subacute or chronic glomerular nephritis.

Clinically, mercuric chloride produces in most cases acute chemical nephrosis, and the picture it produces has become classic. Attention will therefore be paid to this syndrome. The clinical picture is usually one of vomiting, abdominal pain and diarrhea with oliguria or anuria, and whatever urine is passed is usually albuminous, light in color and low in specific gravity, and may contain numerous formed elements including casts and erythrocytes. Elevation of blood pressure may occur, but edema is unusual. Gradually uremia develops and death occurs, or after a period of uremia slow and apparently complete renal recovery results. The clinical picture is at times distinct from that seen in the so-called renal insufficiency of acute nephritis, and the lesions in the kidneys differ widely also. In cases of poisoning with mercuric chloride, the kidneys, which are smooth and soft, appear grossly enlarged. They generally appear grayish white and anemic, suggestive of fatty changes, but some investigators believe that after the eighth day the kidneys are red and congested.

The majority of studies reported in the literature indicate that the kidneys in cases of poisoning by mercuric chloride reveal tubular lesions primarily, and that these lesions include all forms of degeneration and in particular necrosis. Regeneration of epithelial cells occurs, if any cells remain from which regeneration can occur. Deposits of calcium salts in the necrotic cells of the tubules are characteristic of, but not exclusively limited to, poisoning with mercuric chloride.

The glomeruli generally, according to Fahr and Kaufman, are considered to be normal anatomically. Fishberg [20] mentioned that although the glomeruli, apart from congestion, usually appear normal, some swelling and less often foci of necrosis and desquamation of the capsular

18. Suzuki, T., quoted by Aschoff, Ludwig: Lectures on Pathology, New York, Paul B. Hoeber, Inc., 1924.

19. Pearce, R. M.: J. Exper. Med. **18**:149, 1913.

20. Fishberg, A. M.: Hypertension and Nephritis, ed. 2, Philadelphia, Lea & Febiger, 1931.

epithelium may be observed. Held [21] in one case described extensive glomerular changes, consisting of swelling and thickening of the capillary walls, proliferation and desquamation of the epithelial cells of the tuft, which were filled with hyaline droplets, and much exudation in the capsular space. Although such extensive changes are unusual in cases of mercuric chloride poisoning in man, they may occur in the experimental animal. Oliver and Smith [22] reported that in experimental nephritis of frogs, produced by mercuric chloride, the glomeruli were occasionally more injured than the tubules. These glomerular changes consisted of collections of a fibrin-like substance in Bowman's capsule, then formation of a hyaline thrombus within the capillaries, edema and necrosis of the tufts, and hemorrhage into the spaces.

Although "chronic" renal lesions are not produced as a rule by mercuric chloride, such lesions may be produced by other toxic substances, such as uranium, and the experimental work with this substance has led to observations which eventually may be of outstanding importance in a consideration of the pathogenesis not only of renal lesions but also of lesions in other organs. These observations are centered around the fact that in dogs a single dose of uranium of sufficient proportions may produce a "chronic" progressive renal lesion. This observation cannot as yet be applied to cases of nephritis in man, but the possibility of a single insult leading to a chronic progressive lesion presents the basis for a very alluring hypothesis that may eventually explain the pathogenesis of some renal lesions of man.

In the present series are reported three cases of acute chemical nephrosis. The first case followed poisoning by mercuric chloride; in the second case the etiologic factor is unknown, but the clinical picture and the pathologic studies indicated that acute chemical nephrosis existed, and the third was due to chloroform poisoning.

CASE 3.—This was a typical case of mercuric chloride poisoning affecting a young woman who died of acute renal insufficiency (table 2).

At necropsy the right kidney weighed 181 Gm., and the left, 237 Gm.; the kidneys were smooth and purplish red. The capsules stripped easily. On cut sections the edges became everted, and the tissue appeared pink and opaque, but with the markings fairly distinct. Microscopically, the glomeruli appeared normal in size and number. The capillaries were open, although perhaps less blood than usual was within them. There was considerable granular débris in the capsular spaces. The epithelial cells appeared normal, but many were desquamated. The endothelial cells appeared normal, although a few may have been swollen. The glomerular membrane appeared to be in good condition. The convoluted tubules revealed extensive degeneration and necrosis of the cells and complete disorganization of structure. Many of the tubules were dilated and filled with necrotic cells. There were many areas with regenerating tubules and cells with mitotic figures,

21. Held, A.: Ztschr. f. d. ges. Exper. Med. **61**:323, 1928.
22. Oliver, Jean, and Smith, Pearl: J. Exper. Med. **52**:181, 1930.

and the occurrence of more than one nucleus was not infrequent. Fatty change was extreme. There was marked edema of the interstitial tissue, with congestion of the vessels in many areas and occasional collections of a few leukocytes.

Case 4.—In this case which was probably due to mercuric chloride poisoning there developed after operation for supposed carcinoma of the rectum a state of acute renal insufficiency. Because of persistent anemia decapsulation of the right kidney was performed (eleven days before death). The kidney was reported to be pale and somewhat enlarged. Immediately following operation it became very red. There was a slight temporary increase in the urinary output (table 2).

The right kidney weighed 225 Gm., the left, 245 Gm. The right kidney was pale red and smooth, and its capsule had been removed at operation. On cut sections the markings were indistinct, and the cortex measured 0.6 cm. in width,

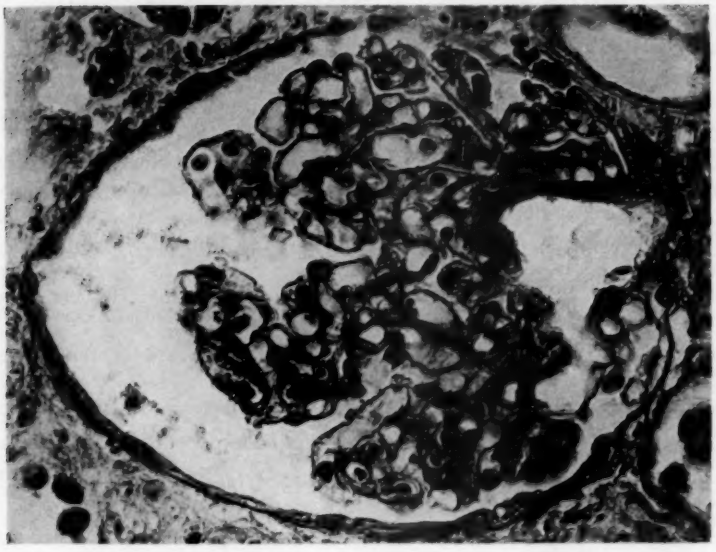
Table 2.—*Significant Clinical and Laboratory Data Noted in Several Cases of Nephrosis*

Case	Cause of Nephrosis	Age, Years, and Sex	Blood Pressure, Mm. of Mercury	Edema	Urine, Vol.	Urinalysis	Hemoglobin	Urea, Mg. in 100 Cc. of Blood	Creatinine, Mg. in 100 Cc. of Blood	Chloride, Mg. in 100 Cc. of Plasma	Cholesterol, Mg. in 100 Cc. of Plasma	Duration of Disease, Days
3	Mercuric chloride, 22.5 grains (0.16 Gm.)	23 F	132/68	±	150 cc.	.....	78%	288	13.2	462	114	7
4	Mercuric chloride (amount before poisoning not known)	56 M	140/76	..	Normal	Sp. gr. 1.036						
	After onset of nephrosis		150/30 190/40	Legs and back ±	75-275 cc. daily	1.010-1.012 albumin 1	28%	112 250 360	20.8	528	...	15 (?)
5	Chloroform 90 cc.	42 F	94/64 74/58	..	45-125 cc. daily	Albumin 2 Pus cells 3	17.1 Gm.	156 186	....	...	...	7
6	Eclampsia	19 F	160/90	+	.....	.....	..	...	....	...	...	2
7	Eclampsia	24 F	.....	0	0	.....	..	57	....	689	...	6 (?)

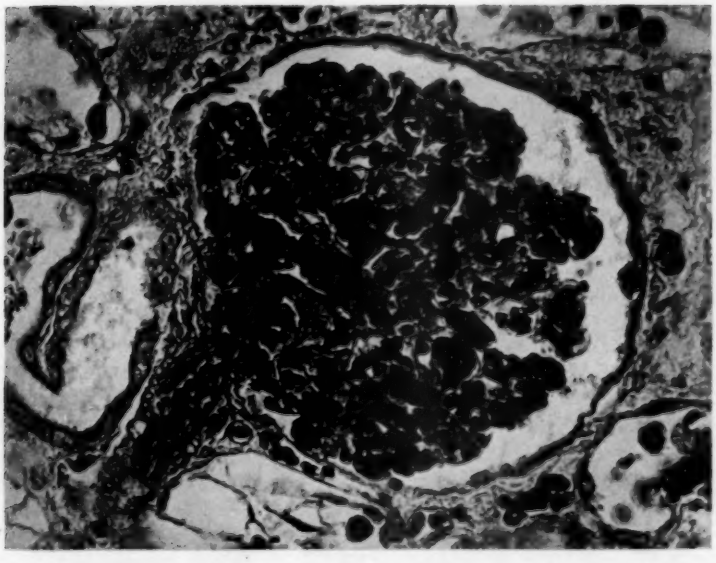
and the medulla, 1.6 cm. The capsule of the left kidney stripped easily and the kidney was light reddish brown; otherwise it was similar to the right.

The glomeruli appeared essentially normal microscopically. Approximately half of them were markedly congested. Some of these congested tufts were in groups, others were scattered, but most of them were nearer to the renal capsule than to the medulla. A few erythrocytes were in the capsular spaces. There was much desquamation of the epithelial cells. The parietal layer of Bowman's capsule contained cells which were somewhat swollen and prominent. The endothelial cells of the tuft were normal in appearance and number, although a few of them may have been swollen. The glomerular basement membrane was essentially normal. It revealed areas of thickening containing nuclei usually near the hilus of the tuft. A distinction between the two kidneys could not be made on the basis of their microscopic appearance.

The tubules were extensively degenerated. In many of them no cytoplasm remained, whereas in others remnants of cells were abundant. Much deeply staining material resembling calcium salts was present. Evidence of regeneration was



A



B

Fig. 3 (case 4).—Probable chemical nephrosis, but cause is unknown: *A*, normal tuft in left kidney (× 400); *B*, normal glomerulus with marked congestion (× 400).

almost lacking. A few tubules were filled with erythrocytes. Few casts were observed. Stains for lipoids revealed a few fat droplets in some of the cells of Henle's loop; occasional loose cells in the tubules were heavily laden with lipoid. The interstitial tissue was markedly edematous with possibly a slight increase in the amount of tissue. A few scattered lymphocytes were seen (fig. 3).

CASE 5 (reported in detail by Olson and Beaver [23]).—This case afforded a classic example of chloroform poisoning with suicidal intent. Jaundice (serum bilirubin, 10 mg. in 100 cc. with the direct van den Bergh reaction) and evidence of hepatic insufficiency in association with acute renal insufficiency were the outstanding clinical features (table 2).

At necropsy the right kidney weighed 152 Gm., and the left, 157 Gm. The kidneys were soft and mottled pink. The liver weighed 1,430 Gm. and was soft.

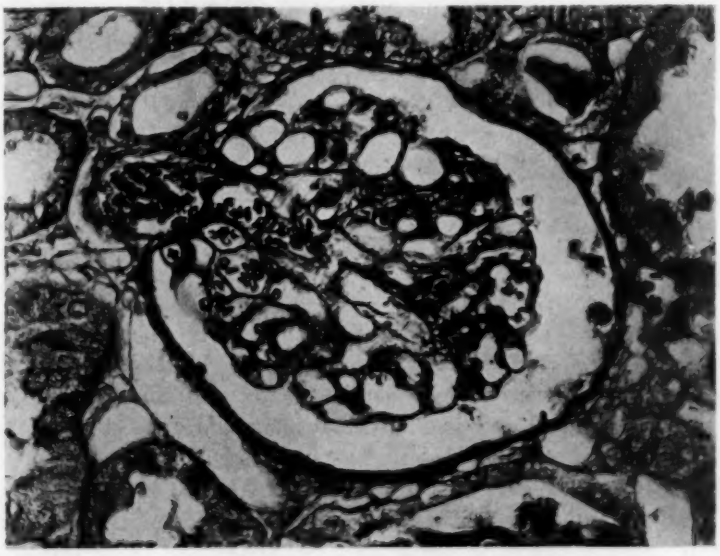


Fig. 4 (case 5).—Chemical nephrosis (chloroform): normal glomerulus (× 325).

On microscopic examination the glomeruli appeared essentially normal except for congestion. The tufts appeared of normal size, and there was very little débris in the capsular spaces. The epithelial cells of the tufts gave evidence of swelling and granular degeneration. The endothelial cells and glomerular basement membrane appeared normal. The tubules revealed varied amounts of degenerative change, with much lipoid in the cells. In some parts the tubules were dilated. In others there was much cellular disintegration, granular in type, although the nuclei were fairly well preserved. Casts were not present. The interstitial tissue revealed occasional regions of slight edema (fig. 4).

Evidences of serious glomerular disease were largely absent in these three cases, although the presence of débris, perhaps coagulated protein

23. Olson, P. F., and Beaver, D. C.: Death from Delayed Chloroform Poisoning, to be published.

in the capsular spaces, the occasional swelling and desquamation of the epithelium, and the glomerular congestion in the second and third cases suggested glomerular aberrations. But the changes were insignificant compared with the tubular alterations. There was no evidence microscopically in case 3 that the decapsulation had produced any permanent anatomic effect on the glomeruli.

It is interesting to speculate with regard to the pathologic physiology of the kidney in cases of poisoning with mercuric chloride. The anuria has been thought by some to be due to mechanical blocking of the tubules and to changes in the capsular epithelium. However, in view of the anatomic findings of blood in the capillary loops, the majority of which are open, it seems much more likely that the explanation offered by Richards [24] is correct. He demonstrated that in the kidney of a frog in which poisoning with mercuric chloride has occurred the glomeruli are extraordinarily active and glomerular fluid is separated at a faster rate than normal, and that this glomerular fluid is apparently of normal quality. Yet urine does not come from the ureter. In Richards' words: "The only explanation which I can reach is that under these abnormal conditions the osmotic pressure of the blood proteins is unobstructed by the normal qualities of the tubular epithelium and is able to draw all or nearly all of the glomerular filtrate back into the blood stream."

Certainly in two of the cases presented here the anatomic observations were compatible with such a hypothesis.

Few studies have been reported of the effects of chloroform poisoning on the kidneys. It is recognized that alteration in the lipoid content of the tubule cells, often manifested as fatty degeneration, is characteristic but not distinctive of this type of intoxication. Clinically, it is well known that patients poisoned with chloroform may demonstrate evidence of renal insufficiency. Whipple and Sperry,[25] and Williamson and Mann [26] have indicated that in experimentally produced chloroform poisoning the liver is the organ chiefly affected, but that other organs, including the kidney, may be injured.

In view of the profound degenerative changes in the liver produced by chloroform poisoning and the well known "toxic" effect on the kidney of the destruction of large amounts of hepatic tissue, as previously noted, it seems reasonable to speculate that in cases of chloroform poisoning a good deal of the apparent renal injury may be secondary to the associated destruction of hepatic tissue.

---

24. Richards, A. N.: Tr. A. Am. Physicians **44**:64, 1929.

25. Whipple, G. H., and Sperry, J. A.: Bull. Johns Hopkins Hosp. **20**:278, 1909.

26. Williamson, C. S., and Mann, F. C.: Am. J. Physiol. **65**:267, 1923.

IV. RENAL CHANGES OF ECLAMPSIA AND PREGNANCY

The renal changes in eclampsia and other abnormal states of pregnancy have been so recently summarized and reviewed by Bell that at present nothing can be added, but confirmation of his results is possible in view of the findings in three cases studied. Bell divided his cases into five groups: (1) typical eclampsia with convulsions, (2) eclampsia without convulsions, (3) preeclampsia, (4) hyperemesis gravidarum and (5) pregnancy associated with preexisting renal disease. In the present study the renal changes in two cases of eclampsia with convulsions and in one case of hyperemesis gravidarum were observed.

The clinical appearance of eclampsia occurs late in pregnancy and is characterized by hypertension, occasionally by edema, albuminuria, oliguria, hematuria (microscopic) and convulsions. Retention of water and chlorides is common, but increase in blood urea is not common, and if present, may be due to renal or so-called extrarenal causes.

Bell, who studied the kidneys in fourteen cases of this type, using Mallory's aniline blue and Heidenhain's azan carmine stain, was able to confirm and extend the findings of Löhlein [27] and of Fahr. Grossly, the kidneys are usually slightly enlarged and their surfaces are smooth. The tissue in cut sections is usually cloudy and pale, although occasionally slightly yellow. Microscopically, the tubules present cloudy swelling or various forms of degeneration and even necrosis. The glomeruli are moderately increased in size, nuclear increase is variable but usually absent, and there is marked thickening of the glomerular membrane, with narrowing of the capillary lumens. This narrowing is due to massive thickening of the capillary basement membrane, which is not homogeneous but composed of parallel layers. Increase in number of the endothelial cells may be slight or striking, and the epithelial cells are only slightly altered, occasionally revealing fine droplets of fat or hyaline granules, but no proliferation. Bell differentiated the glomerular changes in eclampsia from those in clinical acute glomerulonephritis because in the former the "glomeruli are smaller, the basement membrane is much thicker, there are no polymorphonuclear leucocytes, no intracapillary fibers and no epithelial crescents." In glomerulonephritis he also found much more cytoplasm about the endothelial nuclei.

Bell interpreted the increase in number of the endothelial cells as an inflammatory phenomenon, that is, as a form of glomerular nephritis. The thickening of the glomerular membrane, he believed, is more difficult to explain; it may be an inflammatory or a degenerative lesion, the interpretation depending largely on one's definition of inflammation. He classified the lesion as a special form of glomerular nephritis. Others have classified it as nephrosis, considering it to be a degenerative lesion,

27. Löhlein, M., quoted by Bell, E. T.: Am. J. Path. **5**:587, 1929.

and it has also been classified as a separate group, distinct from glomerular nephritis and nephrosis.

Following is a report of two cases of eclampsia:

CASE 6.—The clinical features in this case were characteristic of eclampsia, with convulsions, blindness and anemia (table 2).

At necropsy the right kidney weighed 155 Gm., and the left, 132 Gm. The capsules stripped with ease and the kidneys were smooth, moderately deep red, and on cut sections deep pink. The cortexes were thickened and swollen, and the markings indistinct.

On microscopic examination the glomeruli appeared somewhat lobulated, enlarged and numerous. A moderate number of glomerular loops were open, but erythrocytes were rather scarce. In the capsular spaces a small amount of granular material was present, but crescents were absent. The epithelial cells of the tufts were swollen; some of the cells were very large, granular and pedunculated. Desquamation was frequent. The endothelial cells were increased in number and swollen in many loops; some of the loops were almost filled with several large endothelial cells. This process was not uniformly present. The glomerular membrane was uniformly thickened in most of the tufts, although in a few it revealed only slight, if any, thickening. The convoluted tubules showed moderate cloudy swelling and degeneration. In many areas the tubules were dilated, and granular débris and hyaline casts were present in moderate numbers. The interstitial tissue and vessels appeared normal. Stains for fat revealed scattered tubules containing fat droplets and an occasional glomerulus in which there was a deposit of fat in the endothelial cells of the tuft.

CASE 7.—The clinical features were as characteristic as those in case 6 (table 2).

At necropsy the right kidney weighed 170 Gm. The weight of the left kidney was not recorded. The capsules stripped easily from the renal surfaces, which were smooth and brownish red. On cut sections the markings were exaggerated, although they were somewhat indistinct near the periphery of the cortexes. The cortexes were 0.6 cm. wide, and the medullas were 1.5 cm. wide. The only other significant finding was acute degeneration of the liver.

Microscopically, the glomeruli appeared enlarged, many of them filling the capsular spaces completely. Considerable granular deposit was present in the spaces. The tufts were relatively bloodless, and the individual loops did not seem so wide open as they usually are in normal glomeruli. The epithelial cells of the tufts were swollen and some were desquamated. In most loops the endothelial cells appeared normal, whereas in others there was evidence of proliferation, with even complete obstruction of the loops by huge endothelial cells with abundant cytoplasm. A few intracapillary hyaline fibers were noted. The glomerular membrane was almost uniformly thickened. The thickening was fibrillar. A few loops revealed a membrane of normal thickness. The tubules appeared variable; some were dilated and had flattened, degenerating epithelium; others presented swollen cells, with much granular deposit in the lumens. Deposits of fat occurred in some of the cells of the proximal convoluted tubules. The interstitial tissue appeared normal, as did the vessels (fig. 5).

In the two cases of eclampsia studied, the renal findings were similar to those described by Bell. In both cases fibrillar thickening of the membrane was the oustanding feature in the glomeruli. The

glomeruli were relatively enlarged and relatively bloodless. They practically filled the capsular spaces. In both cases some loops revealed complete obstruction by proliferated endothelial cells, although this feature was not pronounced.

The renal lesion in eclampsia is probably a secondary one, and the kidney is only one of the organs affected. The origin of eclampsia is unknown. The condition is presumed by many to be a form of toxemia, the origin of which may be in the fetus. Another possible source of the toxic substance is the liver. It is known that a diseased liver produces a substance or substances which may lead to degenerative changes in the kidney. The details have been considered in the comment on bile

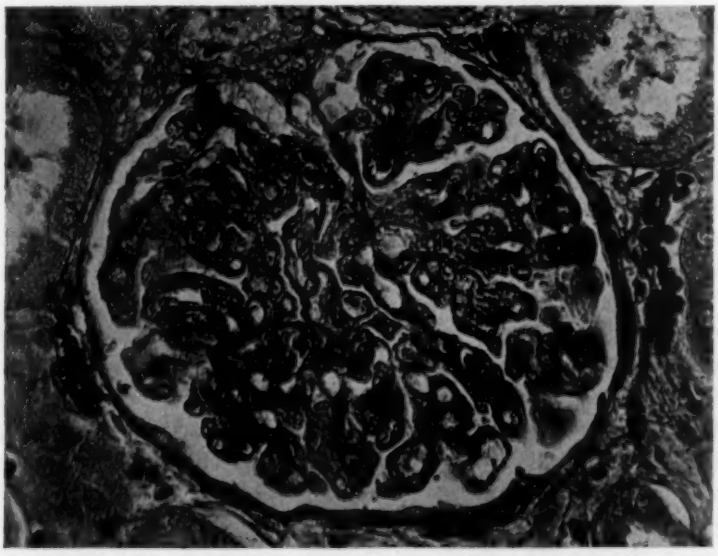


Fig. 5 (case 6).—Glomerulus in kidney of patient with eclampsia: obstruction of loops; relatively large tuft; thickened basement membrane; increase in size and number of endothelial cells of tuft (× 430).

nephrosis. However, the substance generally produced under such circumstances affects the tubules in cases of bile nephrosis, leaving the glomeruli relatively normal, whereas the renal lesions of eclampsia are primarily glomerular.

It is impossible to state the nature of the change in the glomeruli in the present study, but, as Bell pointed out, it is a distinct lesion whether one classifies it as degenerative or inflammatory; since there is a strong possibility that the lesion is purely vascular, secondary to hypertensive and spastic changes, it may not be inflammatory in origin. Perhaps the most interesting speculation regarding the lesion is its probable course following relief of the eclamptic symptoms. The question which

naturally arises is this: If the glomerular membrane is once thickened, does it ever become normal again, or does it remain thickened? As yet, postmortem studies of kidneys from women who have had eclampsia years previously are not recorded in the literature, so this question must for the present remain unanswered. Some data are available which indirectly suggest that when once a change occurs in the glomerular loops and membrane in cases of eclampsia, this change may be permanent. In studying the arterioles of the retina in cases of toxemia of pregnancy, Wagener [28] came to the following conclusions: In early cases with angiospastic changes only, complete recovery without subsequent evidence of vascular disease may occur. However, if organic changes in the vessels and diffuse retinitis develop as a result of more continued or more severe angiospasm, generally persistent hypertensive vascular disease will develop subsequently. It is known that, so far as function is concerned, the kidneys of a previously eclamptic woman return to normal, but experience has shown that moderate anatomic abnormality of the kidney may not always lead to evident functional change. Consequently this occurrence does not answer the question. When it is answered, physicians will know more concerning the nature and significance of the thickening of the glomerular membrane not only in cases of eclampsia but possibly also in cases in which the patients recover from clinical acute glomerular nephritis. It is also to be recalled that among those women with eclampsia who recover, the presence of thickening of the glomerular membrane is merely speculative and it may be that the change is very slight.

The glomerular lesion in eclampsia is so distinct in the sense that it is entirely different from that noted in any of the other forms of nephrosis that this lesion should probably not be classified pathologically as nephrosis. Its exact classification will depend on future observations. However, the renal lesion observed in cases of hyeremesis gravidarum is so similar to that seen in the different forms of nephrosis that it may be so classified at present.

Studies of the kidneys of a patient with hyperemesis gravidarum have been reported previously in this paper. The glomeruli in these kidneys appeared normal, although there was some granular débris in the capsular spaces.

SUMMARY

In this presentation I have described histologic studies of the glomeruli in the kidneys in cases of simple nephrosis in which the diagnosis was made after postmortem study. Cases of simple nephrosis were grouped as acute simple nephrosis, bile nephrosis, chemical nephrosis and renal changes of eclampsia and pregnancy.

28. Wagener, H. P.: Proc. Staff Meet., Mayo Clin. **8**:461, 1933.

A group of ten cases of acute simple nephrosis presented distinct glomerular changes consisting primarily of irregular thickening of the glomerular basement membrane and less often of increase in number and swelling of the endothelial and epithelial cells of the tufts. In the majority of cases these changes were considered independent lesions, the result of associated hypertension, arteriosclerosis or other complicating renal disease. They did not resemble the lesions seen in cases of clinical glomerular nephritis.

In a second group of thirty-one cases of acute simple nephrosis the glomeruli revealed, as a rule, normal tufts with occasional minor variations consisting of variable amounts of débris, usually granular, in the capsular spaces, swelling, degeneration, slight increase in number of the endothelial or epithelial cells of the tufts and occasionally slight, irregular thickening of the glomerular basement membrane. These changes were considered to be probably degenerative, and not suggestive of, or similar to, those observed in cases of glomerular nephritis or lipoid nephrosis.

In a series of thirteen cases of bile nephrosis in which the diagnosis was made at necropsy the majority occurred in persons who presented glomeruli that appeared normal histologically, although a moderate amount of granular material was often noted in the capsular spaces. In six of the thirteen cases slight swelling or proliferation of the endothelial cells of some of the tufts was observed. The epithelial cells of the basement membrane appeared essentially normal. These changes were slight and could not be correlated with the clinical findings, and consequently their significance is doubtful.

In three cases of chemical nephrosis the glomeruli appeared normal except for congestion, desquamation of many of the epithelial cells and granular material in the capsular spaces.

The glomerular changes observed in two cases of eclampsia were similar to those described by Bell; there were moderate increases in size of the tufts, absence of nuclear increase, or a variable degree of it, and marked, irregular fibrillar thickening of the glomerular membrane. In one case of hyperemesis gravidarum the glomeruli appeared normal, although granular material was noted in the capsular spaces. The renal lesion in eclampsia is probably secondary, and although it is distinct and probably degenerative, one is not able to state its nature at present.

ACTIVE AND PASSIVE PLEAT FORMATION OF JOINT CARTILAGE

ERNST FREUND, M.D.
IOWA CITY

The ends of most normal joints are covered with an almost perfectly smooth layer of hyaline cartilage. In later years some irregularities may appear as a result of proliferation and degeneration in the joint cartilage, viz., fibrillation, erosion and even denudation of the subchondral bone, but the unevenness produced in this way is inconsiderable, and the level of the old surface is more or less preserved. I shall consider in this article only the free joint surfaces, exclusive of the joint borders, where in more advanced cases of deforming arthritis large marginal exostoses may develop. More marked deformities of the joint surface may be produced by osteochondritis dissecans after the joint body becomes free or by intra-articular fracture. A part of the end of the joint, with its cartilage and the subchondral bone, may break off, and after reattachment a small steplike deformity may be found at the site of the fracture. Löw-Beer [1] made a histologic study of several intra-articular fractures, but in no case of his series could a real plication of the joint surface be seen. I recently saw an intra-articular fracture of the knee joint in a case of Paget's disease, in which, despite overlapping of the fragments of the joint cartilage, the deformity of the joint surface itself was not pronounced.

In the following pages I shall discuss a type of unevenness of the joint surface in which the folds are large enough to be seen grossly. These folds indicate the presence of some pathologic process which leads eventually to a decrease of mechanical resistance of the joint cartilage.

The process of folding can be either active or passive. Both forms are the result of a disproportion in the dimensions of the bony epiphysis and of its cartilaginous cover. This disproportion may be relative or absolute. It is relative when the total volume of the bony epiphysis becomes diminished by destructive or resorptive processes and the joint cartilage—which is not primarily involved in the process—preserves more or less its normal size. It follows the diminution of the epiphyseal bone with the formation of folds, the apexes of which are directed

From the Orthopedic Department, State University of Iowa, College of Medicine.

1. Löw-Beer, A.: Virchows Arch. f. path. Anat. **273**:191, 1929.

toward the center of the epiphysis. This passive folding of the joint cartilage is thus necessarily combined with a diminution of the volume of the epiphysis; at best, its surface may remain the same, but, as a rule, it will become smaller.

In the active form the disproportion between cartilage and epiphyseal bone arises from augmentation of the volume of the cartilage by extensive proliferative processes in the cartilaginous tissue. By these processes the cartilage becomes too large for the bony epiphysis and forms folds, the apexes of which, different from those already mentioned, are mainly directed toward the joint cavity. By this process of active pleat formation the surface of the entire epiphysis becomes enlarged, but there is practically no change in the volume of the bony epiphysis.

To illustrate the active and passive process of cartilaginous pleat formation, I shall describe briefly a few cases, most of which have been reported before in other connections.

I shall first describe the passive process, which, as has already been indicated, is due mainly to changes in the bony epiphysis, especially in the subchondral zone. Unevenness of the joint surface may also be caused by inflammatory processes in the joints, combined with an increase in intra-articular pressure, necrosis, with softening of the joint cartilage, and porosis of the subchondral bone. These factors may bring about herniation of the joint cartilage toward the bone marrow. This is seen frequently in cases of tuberculous and suppurative arthritis, but it also occurs in animals after injection into the joints of various chemical substances which lead to an exudative arthritis. All these pictures are similar and represent the simplest type of passive formation of cartilaginous pleats. Macroscopically, the formation is barely visible. The microscopic appearance is illustrated by figure 1,[2a] which shows the joint cartilage of a patient with chronic suppurative arthritis, with prolapse of old softened and necrotic joint cartilage toward the subchondral marrow spaces, which have been enlarged by osteoclasts and chondroclasts. Finally, after removal of the zone of preparatory calcification and of the subchondral occluding bony lamella, the marrow spaces may become so large that they are covered only by a thin layer of noncalcified cartilage. This may easily be displaced by the high intra-articular pressure toward the spongy bone, with which it becomes connected secondarily by dense fibrous marrow. In tuberculous joints, in which, as a rule, the undermining of the joint cartilage is more extensive, herniation of the joint cartilage is more frequently observed, but it does not lead to a more marked deformity of the joint surface, because the entire cartilage usually becomes resorbed or sequestrated sooner.

---

2. Freund, E.: (*a*) Virchows Arch. f. path. Anat. **284**:384, 1932; (*b*) **261**: 287, 1926; (*c*) **274**:1, 1929; (*d*) **277**:326, 1930.

Passive folding of joint cartilage is better seen in cases in which slow reorganization of the bony epiphysis takes place, especially if in the process of reorganization the resorption of bone exceeds the formation of new bone. This is the case in aseptic necrosis of the epiphyses, which does not lead to sequestration of the necrotic area (as in osteochondritis dissecans), but to restitution following resorption of the necrotic tissues.

REPORT OF CASES

CASE 1.—An unusual case of aseptic necrosis of both femoral heads was observed in a woman, 77 years of age.[2b] Macroscopically, both heads were flattened, and the joint cartilage showed folding at the apex, as though it were too

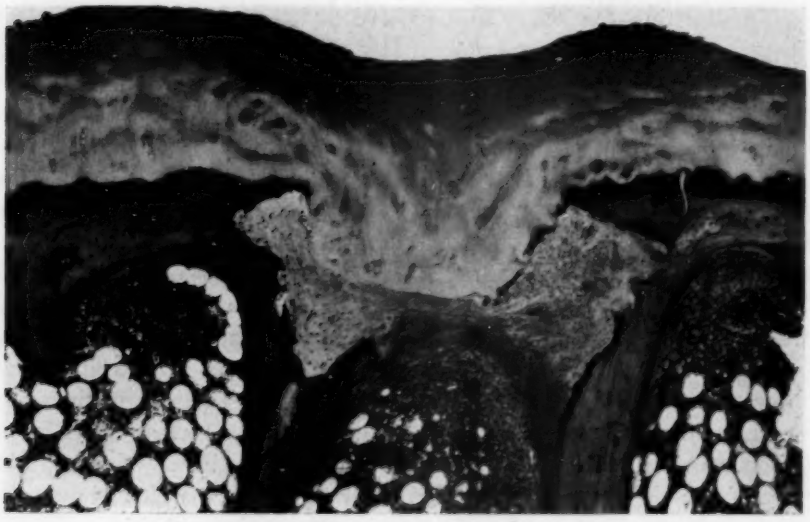


Fig. 1.—Herniation of joint cartilage toward the subchondral marrow spaces in a case of suppurative arthritis. The subchondral bony lamella and the calcified layer of joint cartilage show wide discontinuity; the defect is filled with fibrous marrow toward which the noncalcified cartilage is prolapsing; the joint cartilage is thinned out from above, and its superficial layers are impregnated with fibrinoid substance.

large for the subjacent spongy bone. In both heads the necrosis involved a more or less wedge-shaped area in the subchondral zone. A fracture line passed through the necrotic bone immediately below the joint cartilage and parallel to the joint surface. Although the fracture was old, it showed no signs of healing because it passed for its entire length through necrotic bone which was distant from vascularized living bone marrow.

The continuous friction of the fracture surfaces on each other leads to the accumulation of bone detritus in the fracture space, which gradually becomes massaged into the neighboring marrow spaces. The loss

of bone tissue just below the joint cartilage deprives the latter of its solid support.

However, not only the subchondral fracture, but also a demarcation zone at the borderline between necrotic and healthy bone, weakens the solid structure of the subchondral zone. Necrotic bony trabeculae

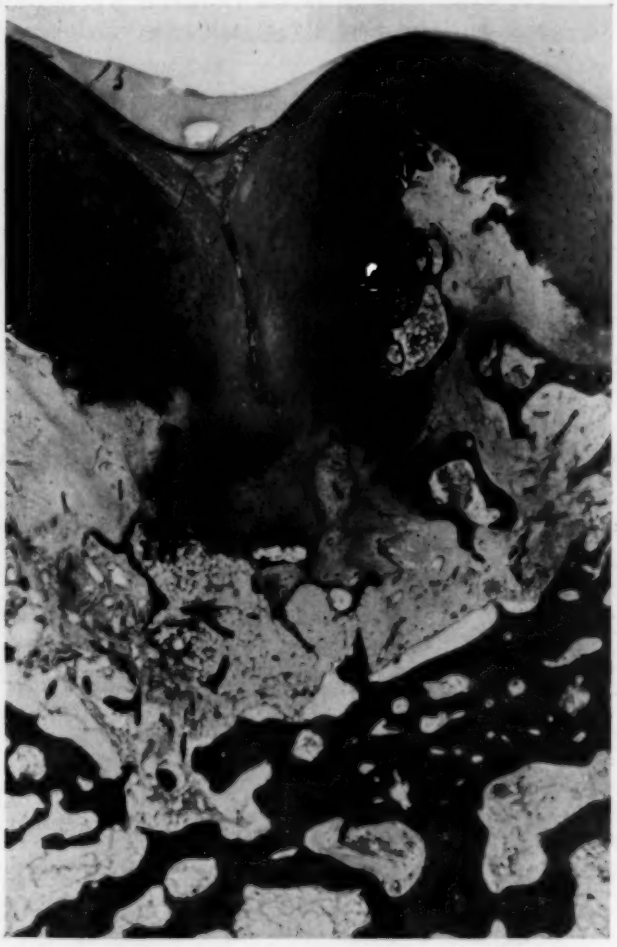


Fig. 2 (case 1).—Deep implication of the joint cartilage in aseptic necrosis of the femoral head. Surface of the cartilage is covered by a fibrous tissue pannus; at the apex of the cartilaginous fold two islands of newly formed cartilage are present in the bone marrow.

become gradually more and more resorbed. Moreover, the formation of new bone does not keep pace with the resorption of bone, and this disproportion leads to weakening of the firmness within the bony epiphysis and to consequences detrimental to the joint cartilage. Finally, after

removal of all the subchondral necrotic tissue, the demarcation zone with its fibrous bone marrow reaches the lower surface of the joint cartilage, and fibrous and cartilaginous tissues grow together. But such a change can be seen only in places with a relatively small extension of the necrosis, especially at its margin, where from the beginning the necrotic area is less extensive in its vertical diameter. In certain areas (fig. 2) the joint cartilage may show arcuate or undulate downward

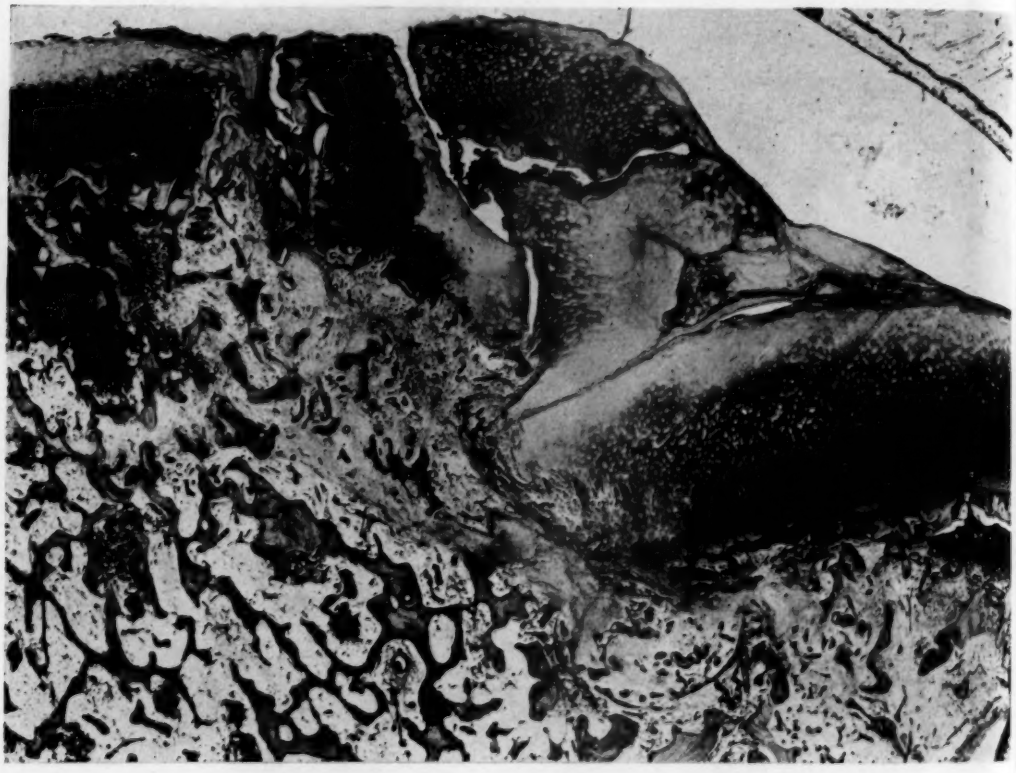


Fig. 3.—Comminuted fracture of the joint cartilage, with displacement and bending of the fragments in same case as in figure 2. The subchondral marrow spaces are shown after resorption of necrotic bone and bone marrow, filled with fibrous tissue, which has also invaded the joint cartilage, bringing about its resorption from below.

displacement. The zone of preparatory calcification and the underlying occluding bony lamella, which are unable to expand because of their rigid consistency, show numerous radial fissures and fracture lines. These traumatic lesions form the first points of attack for the resorption of calcified and even noncalcified cartilage, which thus merges gradually into fibrous bone marrow.

The displacement of the cartilage may be so great in some places that the cartilaginous cover breaks into fragments of different size, forming an irregular heap of cartilaginous bodies (fig. 3). The fibrous bone marrow lies directly below the folded and broken cartilage, which gradually becomes resorbed. Large sinuses form in the deeper layers of the joint cartilage and are partially filled with fibrous tissue. In some places, however, the subchondral fibrous bone marrow shows transformation into cartilaginous tissue. This is especially true where the apex of the cartilaginous fold reaches the underlying fibrous bone marrow or where spongy bone is forming a prominence toward the subchondral fibrous tissue—in other words, in those places where motion of the joint brings about friction between hard substances (as bone tissue and calcified cartilage) and fibrous tissue. It is known that friction and gliding motion are predisposing factors in cartilage formation.

In other areas the cartilage is broken through entirely. The subchondral fibrous tissue grows toward the joint surface through these fractures and fissures in the joint cartilage, forming a fibrous pannus in and around the fracture line of the cartilage. This tends to reunite the fragments. Many small pieces of cartilage and bone are embedded in such a pannus. It is interesting that the pannus, by bridging the valley of the cartilaginous fold, apparently decreases the unevenness of the joint surface. Thus the joint surface may appear smooth, but unevenness exists beneath it.

CASE 2.—I observed essentially the same process of passive fold formation of the joint cartilage, but with fewer signs of trauma, in a woman, aged 71, suffering from Paget's disease (fig. 4).[2e] The case was complicated by fracture of the neck of the femur, and only the broken femoral head showed unevenness of its surface. The entire head was extremely porotic, and practically all of the old spongy bone and the old subchondral bony lamella had disappeared. The joint cartilage was greatly thinned out by resorption from its lower surface, where a layer of fibrous marrow had formed, with bone typical of Paget's disease. The joint cartilage had become deprived of its normal solid support, just as in the patient with aseptic necrosis, but to an even higher degree. Even a slight temporary increase in intra-articular pressure was too great for this bone to withstand, and the joint cartilage easily became displaced toward the marrow spaces in four deep parallel folds.

At the deepest portions of such implications the joint cartilage may again show complete interruption. At these points fibrous bone marrow can push its way toward the joint cavity and cover the joint surface as a pannus. It is of interest that Paget's bone forms in this fibrous tissue on the upper side of the joint cartilage, and so it is possible to find bone marrow typical of Paget's disease and trabeculae with mosaic structure within the joint cavity.

This joint deformity can by no means be called a typical sign of Paget's disease. Against such a supposition is the fact that in the

same case the other femoral head showed a perfectly smooth joint surface, although in its subchondral zone the changes of Paget's disease were more pronounced. The main predisposing factor in the development of such a severe degree of joint deformity is the marked osteoporosis of the epiphysis, which weakens the bony support of the joint cartilage. But the traumatic factor, represented in its simplest form by a temporary increase in intra-articular pressure, is indispensable. I have seen a great number of cases with the highest degree of bone atrophy, especially in the femoral head (after fracture of the neck of the femur), but in none of these was there any cartilaginous pleat formation. I have also seen cases of so-called osteomalacia carcinomatosa, in which most of the bones were almost completely replaced by tumor tissue and formed a mass of soft waxlike consistency. The

Fig. 4 (case 2).—Folding of the joint surface in a case of Paget's disease. The head of the femur shows extreme osteoporosis; the joint cartilage shows fracture lines through which the diseased bone marrow reaches the joint cavity.

patient was bedridden and thus was protected against any considerable trauma, which explains the perfect preservation of the shape of the bones and the joint surfaces.

Case 3.—Probably the highest degree of deformation of the joint surface as a consequence of passive implication of the joint cartilage was shown in a woman, aged 78, suffering from Recklinghausen's osteitis fibrosa (figs. 5 and 6). The right femur showed extreme osteoporosis, with a great number of "brown tumors" in the bone marrow. Fractures were visible at several places, most of which had healed, with marked deformity, although some were of more recent date. An unusual picture was seen at the proximal end of the femur. No normal bone structure was left, and the few irregular and coarse bony trabeculae accompanied by strips of fibrous bone marrow were not able to support the joint cartilage. It was greatly thinned out and in a few places had disappeared. In such places, i. e., surrounding the fovea capitis femoris, the brown bone marrow was covered only

by a thin pannus of fibrous tissue. Owing to the decreased volume of the bony epiphysis, the joint cartilage showed waviness over all the joint surface, in some areas giving the impression that it had become reefed in a regular way, so that it resembled a gathered piece of cloth.

The cause of the fold formation in this case was, as may clearly be seen by the histologic picture, essentially the same as in the case of Paget's disease. There

Fig. 5 (case 3).—Photograph of the head of the femur, showing irregular joint surface and folding of the joint cartilage.

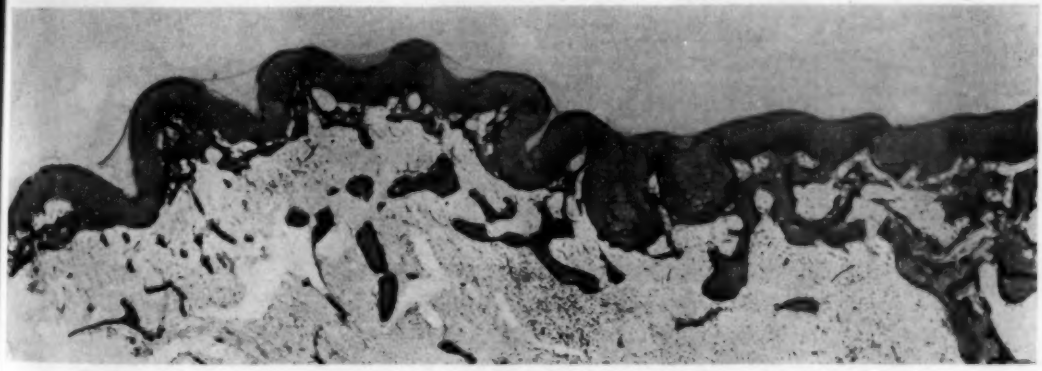


Fig. 6.—Extensive folding of the joint cartilage and markedly porotic bone with "composed" bony trabeculae and fibrous bone marrow in the subchondral zone in the same case as in figure 5. Many of the valleys have become filled with new cartilaginous tissue.

was extreme osteoporosis in the femoral epiphysis, and the subchondral zone was occupied by not very resistant fibrous marrow, with, in greatest part, osteoid fibrous bone. But there were some differences. The displacement which took place in the joint cartilage was not merely passive as was almost entirely the case

in the patient with Paget's disease. There were many reactive changes in the joint cartilage, despite the patient's age. The main feature was the atrophy, which had brought about the marked thinning out of the cartilaginous cover. This could be seen already grossly.

Microscopically, one can follow this process of atrophy in its different stages. The first stage is enlargement of the cell capsules in the more superficial layers of the joint cartilage. The cartilaginous cells proliferate and assume the spindle shape of fibroblasts, or become starlike, and the surrounding hyaline ground substance disappears gradually (Weichselbaum's lacunae, fig. 7). The interlacunar septums become thinner and are finally melted down, and the lacunae merge. By this process large portions of the joint cartilage are lost and are replaced

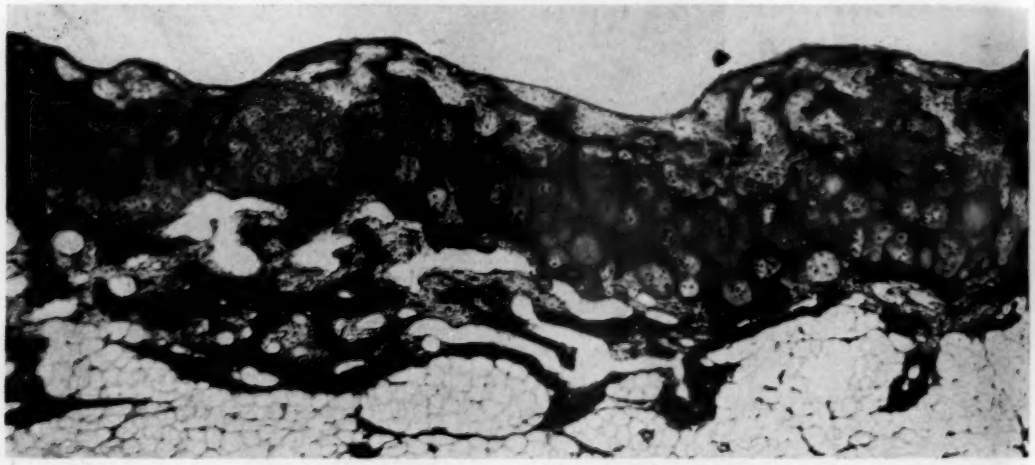


Fig. 7.—Photomicrograph showing: disappearance of joint cartilage by resorption from above and below, confluence of Weichselbaum's lacunae and formation of a loose fibrous tissue pannus on the joint surface, resorption from below by fibrous bone marrow with trabeculae of fibrous bone and proliferative changes of the cells in the deeper layers of the joint cartilage.

in part by loose connective tissue. This becomes vascularized later, forming a connective tissue pannus on the joint surface of the femoral head.

COMMENT

It is of interest that the process of atrophy does not give evidence of catabolism only. Anabolic changes can take place, and the fibrous pannus can again lead to cartilage formation. Then one finds old hyaline cartilage in direct connection with young, extremely cellular cartilage of a more embryonic type. These changes take place especially in the valleys of the uneven joint surface. The production of cartilaginous tissue may be so marked here that the valleys again become completely

filled with cartilaginous tissue (fig. 8). This corrects the unevenness of the joint surface. In other places the waviness is equalized only by the connective tissue pannus, which runs straight over the cartilaginous folds, hiding them completely from above. This explains the difference in counting the folds on the gross specimen and later on the microscopic slide. Grossly, there were only five parallel folds, whereas, histologically, their number amounted in certain places to as many as ten.

If an old person is able to show so many reactive changes in the joint cartilage, one may, of course, expect more in a young person, in whom a combination of active and passive processes in the joint cartilage may yield even more marked deformities.

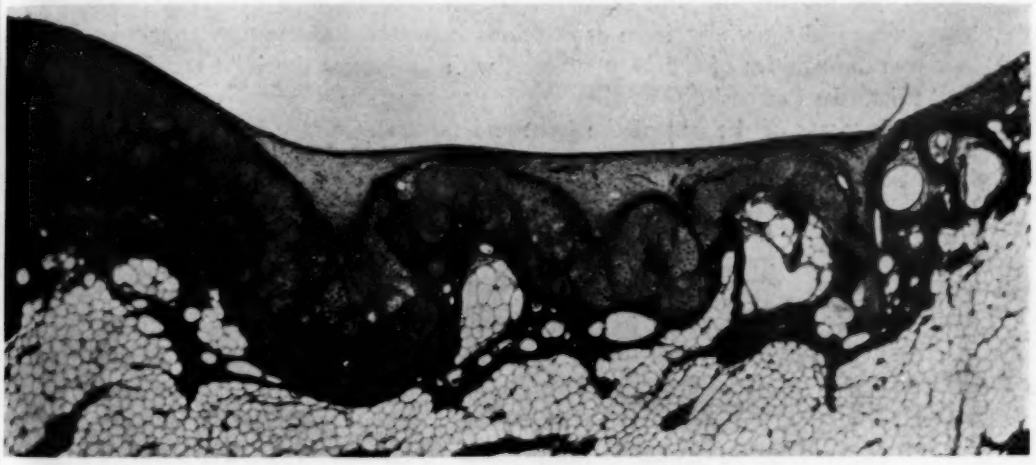


Fig. 8.—Correction of the unevenness of the joint surface by the formation of a fibrous pannus which covers the cartilaginous folds entirely. Active proliferation of the cells of the old joint cartilage followed disappearance of the hyaline ground substance.

In a case of Perthes' disease, for instance, in which the whole femoral epiphysis becomes necrotic and undergoes reorganization, merely passive cartilage implication may occur, especially under weight-bearing and during the active stage of the process. The disproportion in size between the bony nucleus and its cartilaginous cover increases, however, as the process goes on, and this occurs not only by resorption of the necrotic tissues but also by proliferation of the joint cartilage. It is well known that the joint cartilage remains alive in cases of aseptic necrosis of the subchondral bone, deriving its nutrition entirely from the synovial fluids. In a patient with Perthes' disease the joint cartilage is still growing and may be even larger than normal. In normal subjects there is a continuous resorption of cartilaginous tissue from the bone marrow,

owing to the process of enchondral ossification. In Perthes' disease, with its necrotic bone marrow, there is cessation of enchondral ossification of the joint cartilage during the whole period of reorganization. This must lead to an abnormal accumulation of cartilaginous tissue, if the growth of the joint cartilage goes on within normal limits, as it apparently does. The cartilaginous cap of the epiphysis must outgrow the epiphysis and must, therefore, adjust itself to this disproportion by the formation of folds. And, as a matter of fact, roentgenograms in cases of Perthes' disease show, especially in the so-called stage of fragmentation, irregularities of the joint surface indicated by steps and discontinuities in the subchondral bony lamella. The joint space is wider than on the normal side, which is a consequence of the increase in thickness of the joint cartilage. From these signs in the roentgenograms and especially from descriptions in textbooks, one may conclude that deformities of the joint surface, with folding of the joint cartilage, exist. In Perthes' disease they are due to an active and passive deforming process of the end of the joint and especially of the joint cartilage.

This mixed form leads to a discussion of that group of implications of the joint surface which is almost exclusively the result of active proliferative changes in the joint cartilage itself. The changes in the subchondral zone are of little or no importance. I studied this group in its purest form in cases of tabetic arthropathy.

Moritz[3] has shown in his excellent study that reestablishment of the enchondral ossification of the joint cartilage is characteristic of tabetic arthropathies. Enchondral ossification of the joint cartilage can, however, be resumed only in those places where proliferative changes in the cartilage have already taken place. Cartilaginous proliferation is, therefore, a *conditio sine qua non*. The proliferation of the cartilaginous cells is followed by the invasion of well vascularized marrow spaces into the subchondral bony lamella and the zone of preparatory calcification, and, frequently, even into the deep noncalcified layers of joint cartilage. If proliferation takes place in noncalcified cartilage which is in firm union with the deeper calcified layers, the increase of volume can lead only to thickening of the joint cartilage; the cell columns become elongated and thinned out and expand only in one direction. If, however, the solid union between noncalcified and calcified cartilage has become loosened by the invasion of bone marrow in the deeper layers, then the proliferation of the noncalcified layers of cartilage leads not only to an increase in thickness but also to an increase in total area, and the resulting disproportion in size between the proliferative cartilage and the subchondral zone finds expression in an implication or coarse waviness of the joint surface.

---

3. Moritz, A. R.: Virchows Arch. f. path. Anat. **267**:746, 1928.

In one case (tabetic arthropathy with fracture of the neck of the femur),[2d] the active variety of fold formation led to such marked unevenness of the joint surface that several pleats could be seen easily with the naked eye. Figure 9 is a photomicrograph (low power) of the head of the femur, with the characteristic changes. There is elongation of the cell columns and mucoid degeneration of the cartilaginous ground substance—the two most important changes in tabetic joint cartilage. Half of the cartilaginous folds are directed toward the joint cavity, and the alternate half toward the subchondral spongy bone. One might think that one was dealing here with passive pleating of the joint cartilage which had been displaced by trauma, as in the group previously mentioned. But this supposition may be excluded because: (1) the proliferating and thickened cartilage blends gradually with the old cartilage,

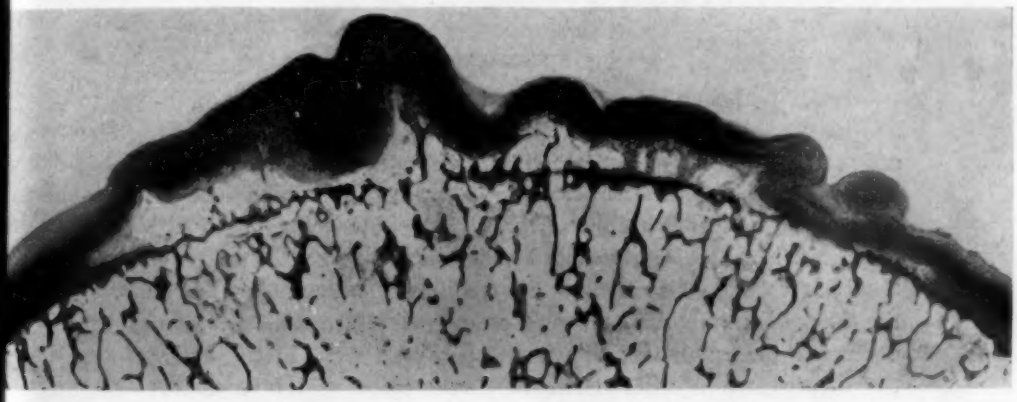


Fig. 9.—Active process of fold formation in a case of tabetic arthropathy. The subchondral bony lamella with parts of the zone of preparatory calcification is preserved; the noncalcified cartilage is invaded by marrow spaces and shows active proliferation of its cell groups with consequent fold formation. Cartilage formation is present in the pannus on the joint surface.

which is firmly united with the subchondral spongy bone, the cells of which are perfectly quiescent, and (2) the subchondral bony lamella remained in place, together with parts of the zone of preparatory calcification, thus forming a good landmark to show where the joint cartilage once ran and how it became elevated and formed folds to accommodate its lateral expansion (*Flächenwachstum*).

There is another feature of this case which shows clearly that the unevenness of the joint surface is due to proliferation of the cartilage. In one place the deeper layers have been resorbed by bone in such a way that the cartilage became undermined for a considerable distance by large marrow spaces. These marrow spaces are in the stage of obliteration by the implication of the joint cartilage toward the preserved

subchondral hard substances. The marrow of the intracartilaginous marrow spaces becomes in this way compressed and transformed into dense fibrous tissue, which in some places undergoes transformation into fibrous cartilage. In no place can signs of traumatization be seen. All the changes may be explained by the high activity and the power of proliferation of the tabetic joint cartilage, with subsequent invasion by marrow spaces.

As to the practical value of these observations in the group of cases showing passive fold formation as well as in that showing active fold formation, it is clear that the process leading to such marked deformities must be detrimental to action of the joint. This is especially true in younger persons, when the underlying disease is not fatal *per se*. In cases of Perthes' disease, I found, as a rule, an early onset of hypertrophic arthritic changes in the hip joint.

SUMMARY

Under pathologic conditions the joint cartilage may show more or less marked plication. The process leading to this unevenness may be active or passive, the latter being by far the more frequent. Both forms result from a disproportion in the dimensions of the bony epiphysis and of its cartilaginous cover. If the total volume of the bony epiphysis becomes diminished by destructive or resorbing processes, the joint cartilage may follow the diminution of epiphyseal bone, with the formation of folds, the apexes of which are directed toward the center of the epiphysis; this is the passive type. In the active form the disproportion between cartilage and epiphyseal bone arises from augmentation of the cartilaginous volume by extensive proliferative processes in the cartilaginous tissue. By these changes the cartilage becomes too large for the bony epiphysis and forms folds, the apexes of which are directed mainly toward the joint cavity.

HISTOLOGIC CHANGES IN THE KNEE JOINT IN VARIOUS INFECTIONS

CHESTER S. KEEFER, M.D.
FREDERIC PARKER JR., M.D.
AND
WALTER K. MYERS, M.D.
BOSTON

In previous articles we [1] described the changes observed in the knee joint with advancing age. It was pointed out that an increased number of anatomic alterations were seen as age advanced and that the gross and microscopic examination of these lesions showed changes characteristic of the various stages of so-called degenerative arthritis. As these observations defined the type of lesion resulting from a degenerative process, we studied the knee joints of eight patients with infections of the joint cavity in order to compare the changes in an inflammatory lesion of the joints with those resulting from a degenerative process. There were two cases of gonococcic, two of hemolytic streptococcic, two of meningococcic and one of pneumococcic, infection and one showed an unidentified gram-negative coccus causing subacute bacterial endocarditis and arthritis.

GONOCOCCIC ARTHRITIS

CASE 1.—A man, aged 42, was admitted to the hospital with pain in the knees of eight weeks' duration. He had a similar attack of polyarthritis following gonorrhea three years before admission. On examination, he showed psoriasis, chronic gonococcic urethritis and an acute arthritis of both knee joints. Gonococci were obtained from the urethral discharge, and the complement-fixation reaction of the blood was positive with a gonococcus antigen. Five days after admission he had a chill, and signs of lobar pneumonia developed in the lower lobe of the right lung. During the course of the pneumonia the psoriasis disappeared. He failed progressively and died six days after the onset of the pneumonia.

Necropsy showed the lesions of a typical pneumococcic lobar pneumonia and the following changes in the joints: On opening the knee joints there was no excess fluid. The patellas appeared normal. The femoral and tibial condyles were

---

From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), the Department of Pathology, Boston City Hospital, and the Department of Medicine, Harvard Medical School.

1. Keefer, Chester S.; Parker, Frederic, Jr.; Myers, Walter K., and Irwin, Ralph: Arch. Int. Med. **53**:325, 1934; Parker, Frederic Jr.; Keefer, Chester S.; Myers, Walter K., and Irwin, Ralph: Arch. Path. **17**:516, 1934.

likewise smooth and showed no areas of destruction, although the thickness of the cartilage over the lateral condyles of the tibia was decreased. The synovia appeared somewhat thickened; the surface was smooth except in several small areas where it was dull and irregular.

Microscopic examination of the synovia from the right knee joint showed a slight irregularity of the surface where the superficial layer of cells varied in thickness. There were no definite papillary projections. In the connective tissue layer there was a marked infiltration with polymorphonuclear leukocytes, lymphocytes and macrophages with an intense congestion of the blood vessels. An occasional macrophage filled with blood pigment was seen. In several foci there was a partial loss of the superficial synovial cells with a deposit of fibrin. In places the collagen and polymorphonuclear leukocytes appeared necrotic. A careful search of the tissue, stained for bacteria, failed to reveal their presence.

The synovia from the left knee joint showed an infiltration with some polymorphonuclear leukocytes, lymphocytes and macrophages. In some areas the connective tissue was edematous; in others it was dense. Over the surface the synovial cells were thin and flat. The vessels were prominent and seemed to extend closer to the surface than usual. No organisms were demonstrated.

In this case, the principal lesion was in the synovial tissues and was characterized by an inflammatory reaction which had extended to the surface of the synovia in some places. In other words, it was a synovitis beginning in the synovial connective tissues.

The following case was a much more advanced stage of the same type of infection:

CASE 2.—A man, aged 50, was admitted to the hospital on account of pain and swelling in the left knee joint. He had had a chronic urethritis for a number of years. On examination, he showed a bilateral catarrhal conjunctivitis, slight fever and an arthritis of the left knee joint. This joint was swollen, painful and tender. The overlying skin was red and the surface temperature increased. The patella was elevated, and there was definite fluctuation of the joint capsule. The urethral discharge showed many gonococci, and fluid aspirated from the left knee joint had the characteristics of an exudate; gonococci were seen on smear and grown in culture. During the period of observation the patient continued to have high irregular fever and leukocytosis; and, in spite of repeated aspirations, the fluid continued to accumulate in the joint. The blood cultures were sterile. Within two weeks, 1,065 cc. of purulent fluid was removed from the left knee joint. The patient became progressively weaker and died one month after admission.

Necropsy showed a bilateral hydrothorax and a purulent arthritis of the left knee joint. Examination of this joint showed that it contained an excess of mucopurulent exudate. The bursae communicating with the joint were likewise filled with purulent material from which gonococci were recovered. The proximal tibiofibular joint was likewise filled with a similar exudate. The synovial membrane was swollen, thickened and markedly injected. The surface was rough, dull and covered with exudate. The articular cartilage of the patella showed fibrillation of the cartilage of the median horizontal facets such as is seen in many patients of this age. On the articular surface of the femur there were erosions on the patellar groove and on the lateral and medial condyles. The tibia showed thinning of the cartilage over the areas of pressure. In no place was there evidence of destruction of the cartilage by the inflammatory process in spite of the fact that the infection had been present for several weeks.

Histologic examination of the synovial membrane revealed that the superficial synovial cells were absent and that they had been replaced by granulation tissue containing numerous lymphocytes, polymorphonuclear cells, macrophages and plasma cells. In the deeper layers of the synovia there was a perivascular infiltration of lymphocytes. The sections stained for bacteria showed numerous gram-negative cocci which were undoubtedly gonococci, since this organism was recovered from the tissue on culture.

The changes observed in this knee joint were those of an acute synovitis without any striking alteration in the cartilage or bone.

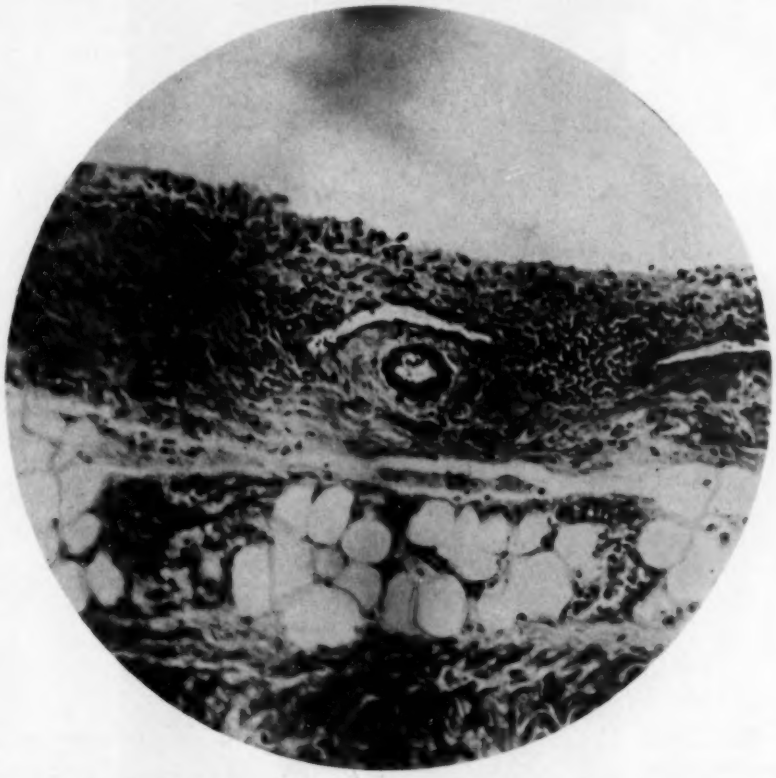


Fig. 1 (case 1).—The synovial membrane from a patient with gonococcic arthritis showing the inflammatory reaction beneath the superficial cells of the membrane (× 170).

In these two cases the reaction differed in intensity. In the first case, no gonococci were recovered from the joints at necropsy, and no organisms could be found in the stained sections. In the second case gonococci were grown from the exudate and found with ease in the stained sections of the synovia. These two cases represent what is often seen clinically, namely, a type of arthritis associated with definite gonococcic infection of the urethra or other parts of the genito-urinary

tract in which gonococci either are not found or are rarely grown from the joint fluid, and a second type in which there are many gonococci in the fluid. As a rule, as far as complete recovery from the joint disorder is concerned, the outlook is better in the former and the reason seems plain from the character of the histologic changes in the joints. That is to say, the inflammatory lesions are less intense and are characterized by an infiltration of polymorphonuclear leukocytes, lymphocytes and plasma cells. The surface

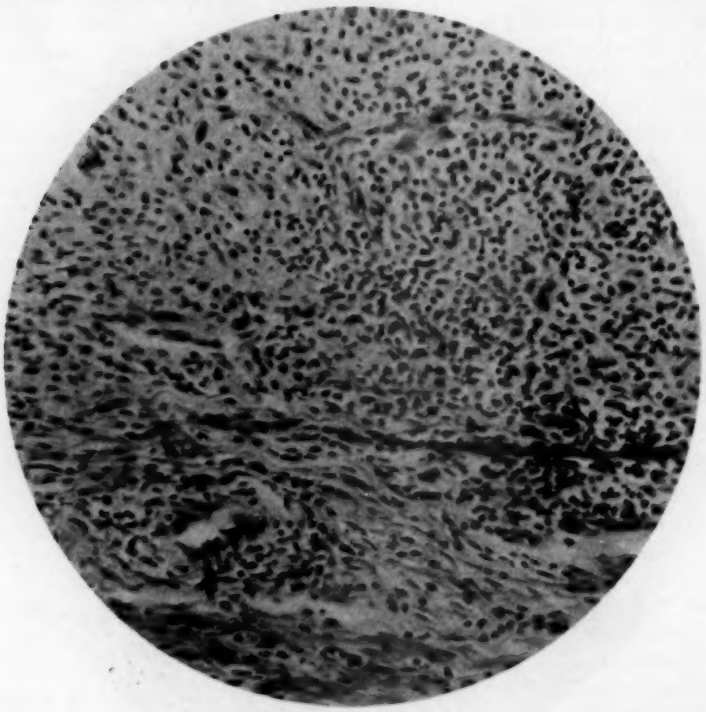


Fig. 2 (case 2).—Synovial membrane showing infiltration with leukocytes and complete destruction of the superficial synovial cells (× 95).

layer of the synovia remains intact and shows no areas of destruction (fig. 1). This picture contrasts strikingly with the observations in case 2 in which the synovial lining was completely destroyed and replaced by granulation tissue containing lymphocytes, polymorphonuclear cells, macrophages and plasma cells (fig. 2). Accompanying these changes were areas of perivascular infiltration of lymphocytes. In other words, in the first case the prominent lesions were beneath the surface of the synovia, whereas in the latter they extended to the surface and produced complete destruction of the superficial cells.

STREPTOCOCCIC ARTHRITIS

CASE 3.—A white woman, aged 76, was well until three weeks before admission when she fell and injured her right knee. This was soon followed by pain and swelling which continued until admission. On examination it was found that she had fever, moderate senile kyphosis and generalized arteriosclerosis. The right knee was swollen, hot, tender and painful. Otherwise, no striking abnormalities

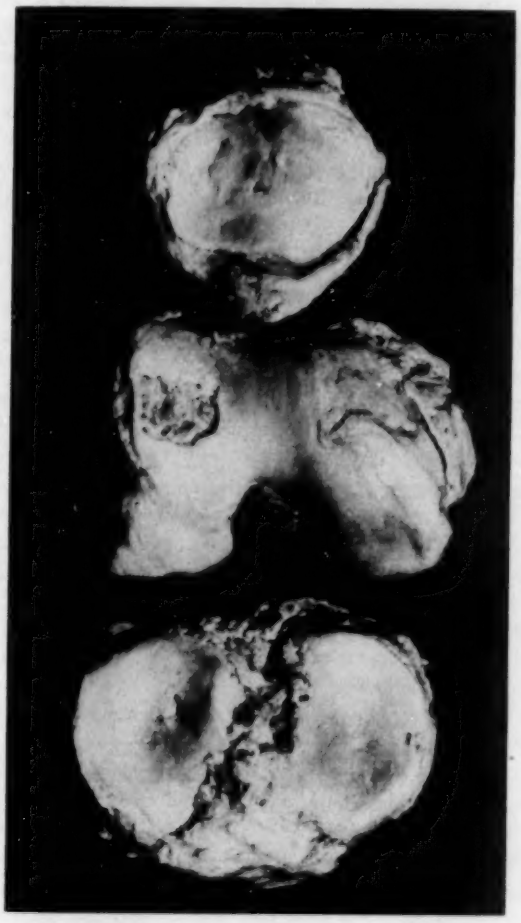


Fig. 3 (case 3).—Gross specimen of knee joint from a patient with streptococcic osteomyelitis and arthritis.

were found. The temperature varied between 98.6 and 102 F.; the patient gradually became stuporous and incontinent; signs of bilateral bronchopneumonia developed and death occurred five days after admission.

The white cell count varied from 6,700 to 16,100 per cubic millimeter with 82 per cent polymorphonuclear leukocytes; the blood culture was positive for Streptococcus haemolyticus.

Necropsy showed a septic arthritis of the right knee joint, osteomyelitis of the right femur, bilateral bronchopneumonia and generalized arteriosclerosis. Cultures of the blood and right knee joint showed hemolytic streptococci.

On opening the right knee joint the synovia appeared dull gray and projected over the edge of the patella. The fluid was mucopurulent and contained many micro-organisms. The patella showed marked erosion of the cartilage so that it was thinned over the lateral facet. The same was true of the cartilage over the median facet. The articulating surface of the femur showed thinning of the cartilage, and on the lateral surface of the patellar groove there was an irregular area measuring 1.5 by 1.5 cm. which extended through the subchondral bone into the marrow. There was a focus of osteomyelitis that had perforated into the joint cavity. The synovial membrane about the femur was greatly thickened and was continuous with granulation tissue which extended over the surface of the bone.

The articular surfaces of the tibia showed marked thinning of the cartilage with areas of irregularity, especially over the points of greatest pressure. These gross changes are shown in figure 3.

The left knee joint showed no signs of infection, but there were erosions over the middle portion of the patella, the patellar groove of the femur and the articulating surfaces of the tibia.

Microscopic examination of the synovia showed that in places there was a complete destruction of the membrane down to the fat tissue and the large nerves. The exudate was composed mostly of polymorphonuclears, with some lymphocytes, macrophages and plasma cells deep down in the tissue. The endothelium of the blood vessels showed proliferation.

The bone showed many abscesses in the marrow. While the bone was not apparently necrotic, it was being dissolved. This process involved the cartilage also. At one point the cartilage had almost completely disappeared, and the process extended across the surface with diminishing intensity; that is, there were necrosis and disappearance of cartilage and infiltration with many polymorphonuclear leukocytes; then solution of the superficial cartilage with invasion of the necrotic cells by polymorphonuclear cells; then masses of bacteria and no leukocytes, with necrosis of adjacent cartilage cells. The organisms were shown by culture to be hemolytic streptococci. They were most numerous in the advancing portion of the lesion (fig. 4).

This patient had an osteomyelitis of the lower end of the femur which had perforated into the right knee joint and produced an infection of the synovia with destruction of cartilage and bone.

Case 4.—In a young man with a deformity resulting from a healed poliomyelitis a trophic ulcer developed about the left knee joint. This became infected with hemolytic streptococci, and the infection spread into the joint cavity by direct extension. It became necessary to amputate the leg above the knee.

The knee joint showed that the condyles of the femur were small and not well developed. The depth of the patellar groove was shallow. The synovial membrane was thickened and covered the posterior aspect of the patella almost completely. It was also adherent to the lateral condyle of the femur and extended into the joint cavity at this point. Over the articular surface of the median condyle of the femur there was a superficial erosion of the cartilage with irregularity of the surface due to fibrillation. Over the corresponding articular surface of the median tibial condyle there was erosion of the cartilage.

The semilunar cartilages were small and irregular, showing numerous irregularities and tears with fibrosis and evidence of a process of repair progressing in the torn areas.

The synovial membrane was thickened, and a large part of the surface of the membrane was destroyed. In areas where the synovial cells were present, the lining consisted of rather large cells which were covered here and there with fibrin. Beneath the surface there was a marked infiltration of lymphocytes and macrophages containing hemosiderin. The connective tissue was vascular, appeared young and was infiltrated with a considerable number of leukocytes. In some

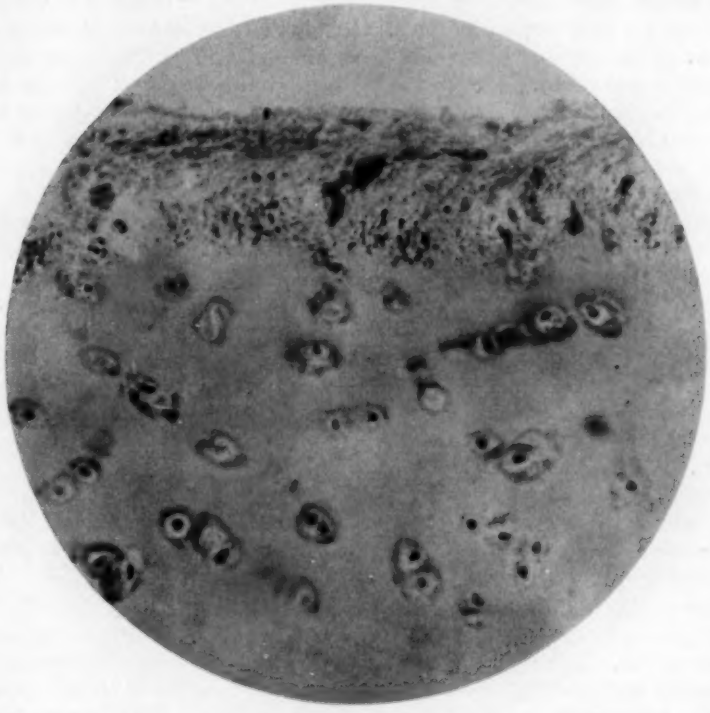


Fig. 4 (case 3).—The superficial layer of cartilage shows beginning destruction due to the advancing streptococcic infection (× 95).

areas the synovial lining was completely destroyed and replaced by a dense layer of granulation tissues infiltrated with numerous plasma cells and polymorphonuclear leukocytes. Beneath these areas there was a marked perivascular infiltration of lymphocytes and plasma cells. The connective tissue also appeared young and was edematous. The capsule did not appear abnormal.

MENINGOCOCCIC ARTHRITIS

There were two patients with meningococcic meningitis and arthritis; one was 34 years of age, and the other, 42. The clinical history and anatomic findings in the knee joints were as follows:

CASE 5.—A white man, aged 34, was admitted to the hospital with headache and signs of meningitis. The spinal fluid showed the characteristics of purulent meningitis, and meningococci were seen on smear and grown by culture. Thirteen days after admission the patient complained of pain, tenderness and slight swelling of the left elbow joint. There was no redness. At no time did he complain of pain in the knee joints. He died twenty-one days after admission. The elbow was not obtained at autopsy, but both knee joints were opened and material removed for examination.

The right knee joint was normal in appearance and contained no excess fluid. The surfaces of the joints appeared smooth and glistening. The median surfaces of the patellas were smooth; the lateral surfaces showed an elevation of the border which was due to a thinning of the articular surface of the cartilage, pressing the cartilage at the edge outward. The synovial membrane extended over the edge as papillary projections. The femoral surface showed that the lateral condyle was normal; the medial condyle showed a defect 2 by 3 mm. and corresponded to the area which came in contact with the intercondyloid tubercle of the tibia. The tibial surface was smooth; the capsule was not thickened. In no area was there evidence of destruction of bone or cartilage by inflammation.

Microscopic examination of the synovia showed that the surface was intact and smooth. The tissue between the superficial layer of synovial cells and the deeper layers of the synovia showed a marked infiltration with polymorphonuclear leukocytes, a few lymphocytes and occasional mast cells. There was one thrombosed blood vessel with an infiltration of polymorphonuclear cells, and in another area a perivascular infiltration with polymorphonuclear leukocytes without fibrin or necrosis. A section stained for bacteria by the MacCallum-Goodpasture method showed beneath the superficial layer of cells focal collections of polymorphonuclear leukocytes, macrophages and numerous gram-negative diplococci, mostly extracellular.

In other words, micro-organisms could be demonstrated in the connective tissue of the synovia, and there was the reaction of acute inflammation about the bacteria. In this case, the infection was so slight that it did not extend to the surface cells and cause an effusion into the joints.

CASE 6.—A white man, aged 42, was admitted to the hospital with a sore throat, pain in the neck and in both knees, numbness of both legs, general malaise and prostration. These symptoms had been present for two days and were ushered in abruptly with a chill. On admission the patient was conscious but extremely ill. The temperature was 104.4 F.; the white cell count, 26,500 per cubic millimeter. Signs of meningitis were present, and the cerebrospinal fluid was characteristic of a purulent meningitis. Meningococci were grown from the blood and spinal fluid. The patient died on the third day of his illness.

The right knee joint did not contain an excess of fluid, and the synovia appeared smooth without evidence of acute inflammation. At the border of the patella there was a tendency for the synovia to extend over the edge and encroach on the articular surface. The femoral and tibial condyles were smooth and, aside from a slight thinning of the cartilage over the articular surface of the tibia, no abnormalities were observed. The left knee was similar in all respects to the right. On microscopic examination the synovial membrane showed two types of lesions. The first was characterized by changes confined entirely to the connective tissue beneath the thin layer of synovial cells. The surface of the synovial membrane was smooth and intact, the cells appearing normal. In the connective tissue there were numerous areas showing infiltration with polymorphonuclear cells, a

few lymphocytes and mast cells. These cells were concentrated about the smaller blood vessels just beneath the surface and between the strands of connective tissue. A few of the areas of infiltration were situated quite deep in the tissue, and here again the cellular infiltration was noted, especially about the blood vessels.

A more advanced stage of this process was noted in some of the sections. The superficial synovial cells appeared swollen and pale and, in many places, necrotic. In other areas, they had disappeared entirely, leaving a surface composed of granulation tissue and a thick layer of cellular exudate composed of polymorphonuclear

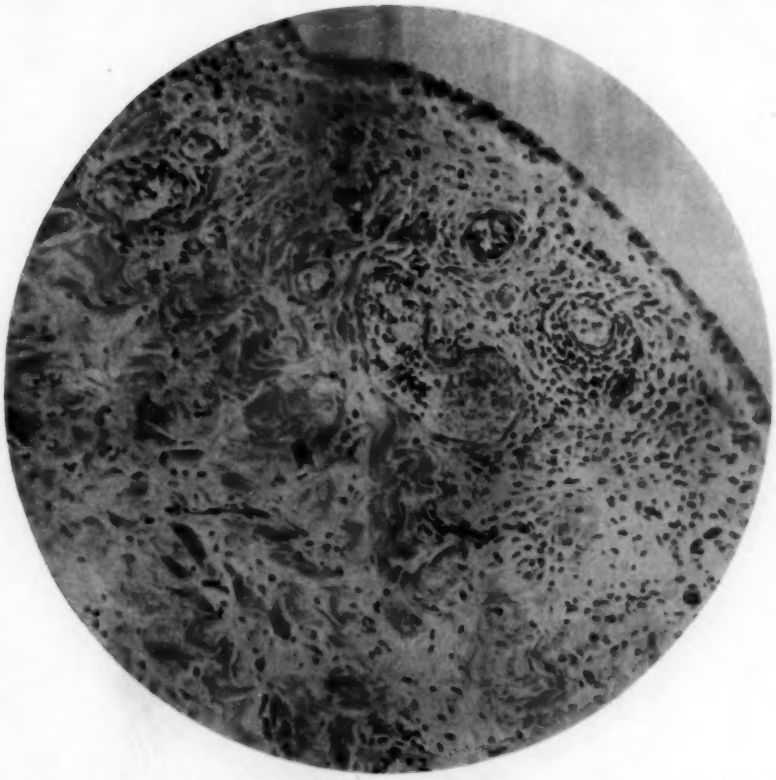


Fig. 5 (case 5).—Synovial membrane from a patient with meningococcic arthritis showing the early lesions with focal collections of cells about the blood vessels and in the connective tissue (× 170).

leukocytes. At this stage the perivascular arrangement of the leukocytes was not striking, although here and there this could be seen. In spite of the intensity of the reaction at the surface, it was almost entirely limited to this location and did not extend far into the capsule. There were collections of cells here and there quite deep in the synovia, but they were few. A stain showed a number of diplococci in the area showing the inflammatory reaction.

The course of events in meningococcic infection of the synovia is as follows: The organisms reach the synovia by way of the blood stream

and are deposited in the connective tissue beneath the surface of the synovial membrane. This is followed by collection of polymorphonuclear cells, lymphocytes and plasma cells, especially about the blood vessels and between the strands of connective tissue. At this stage the synovial cells on the surface remain intact. Later as the infection progresses there is a disintegration of the synovial cells, and the surface is replaced by a layer of granulation tissue and numerous polymorpho-

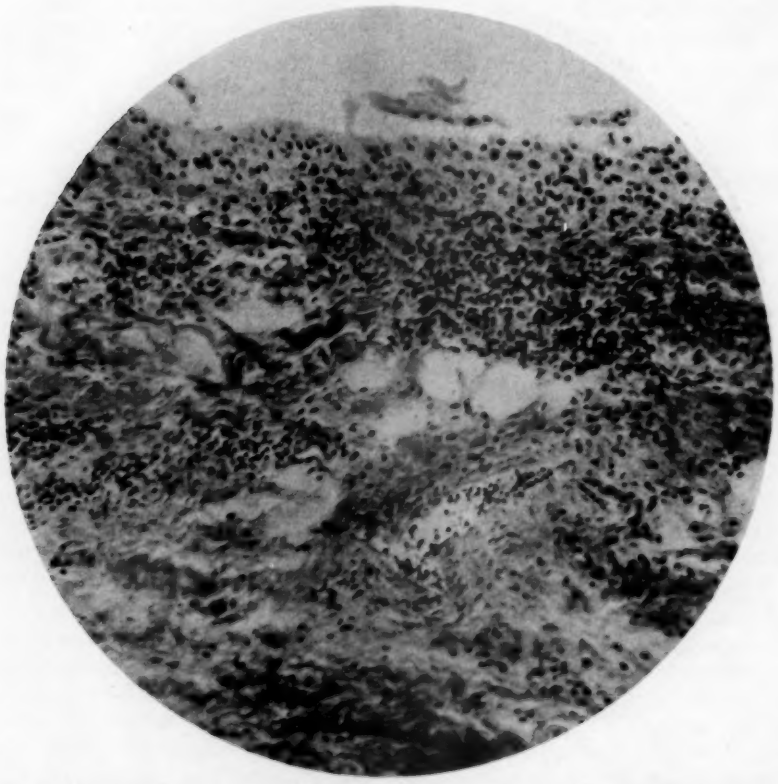


Fig. 6 (case 5).—Synovial membrane from a patient with meningococcic arthritis showing infiltration of superficial areas with polymorphonuclear leukocytes, lymphocytes and plasma cells (× 170).

nuclear leukocytes. The process does not extend deeply into the capsular tissue. The essential lesion is then one of an acute synovitis (figs. 5, 6 and 7).

It has been noted previously that pains in the joints are extremely common in both the acute and the chronic form of meningococcic sepsis, with or without meningitis. The clinical features of this type of infection of the joint have been described by numerous writers. As

a rule, arthritis occurs in about from 4 to 7 per cent of the cases of meningococcic meningitis. Herrick and Parkhurst [2] divided the cases into three groups. In type A they included the cases in which polyarthritis was a feature of meningococcic sepsis at the onset of the disease and usually disappeared after the third day of the illness. Associated with the pains in the joints was the characteristic rash of meningococcic sepsis. The pains in the joints were usually accompanied by

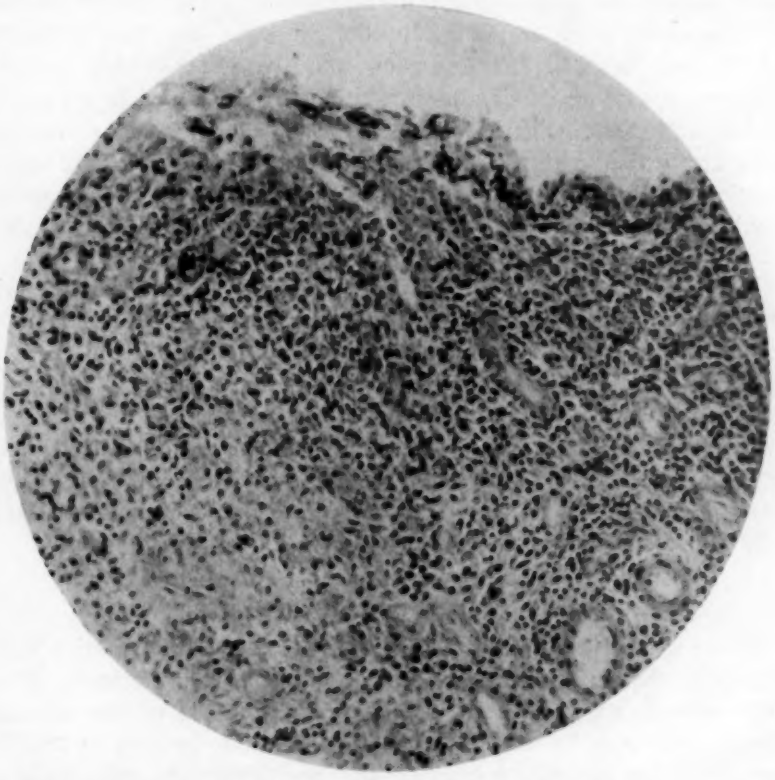


Fig. 7 (case 6).—Synovial membrane showing extensive inflammatory reaction with infiltration and destruction of the superficial areas (× 170).

tenderness but no swelling. It was not possible to obtain fluid from the joint for examination owing to an absence of an increased amount of fluid. In some of their cases meningitis did not appear, but other metastatic lesions such as panophthalmitis, epididymitis or pericarditis were observed. Sometimes the blood culture was positive, and if so the mortality was high. As many patients with pains in the joints

2. Herrick, W. W., and Parkhurst, G. M.: Am. J. M. Sc. **158**:473, 1919.

have a hemorrhagic rash, Herrick and Parkhurst postulated that the pains are probably due to hemorrhage into the joints and joint tissues. In case 2 of this study the pains in the joints were undoubtedly similar to those just described; the blood culture was positive, and the patient died on the third day. There were no hemorrhages into the joints or joint tissues, but the pain was without doubt due to the inflammatory lesions in the synovial tissues where the organisms were located.

In the second group, called "B" by Herrick and Parkhurst, the joints, usually the large ones, were the site of a suppurative process which appeared about the fifth day of the illness. This was characterized by pain, swelling and effusion into the joints which had the characteristics of an exudate and contained meningococci in about one third of the cases. The lesion was thus metastatic, such as occurred in the first group, with the difference that it was usually a more severe infection of the joint and produced effusion. Recovery was usually complete in about from one to four weeks, although ankylosis occurred occasionally when there was necrosis of the bone.

The third type of pain in the joints described by Herrick and Parkhurst was the arthralgia of serum sickness which appeared in some of the patients following the administration of therapeutic serum.

It is plain from the previous clinical descriptions and from our histologic observations that meningococcic arthritis is a metastatic lesion involving first the deeper synovial tissues. Later the infection invades the superficial cells with effusion of fluid into the joint cavity and varying degrees of destruction of the cartilage. It is, indeed, essentially a metastatic acute synovitis.

ARTHRITIS OF SUBACUTE BACTERIAL ENDOCARDITIS

Pains in the joints occurring during the course of infective endocarditis of the subacute variety are far from being uncommon. Curiously enough, we have been unable to find records of the anatomic changes that may be seen. This is probably due in part to the fact that the joints do not suppurate and are, therefore, not examined post mortem.

In the following case of subacute bacterial endocarditis due to an unidentified gram-negative coccus, there were pains in the joints during life, and slight changes in the synovia were observed at necropsy.

CASE 7.—A man, aged 25, complained of dyspnea on exertion. Five months before admission he had pains in the knee joints suggestive of mild rheumatic fever. Otherwise his past history was irrelevant.

On examination it was found that he had fever, leukocytosis, the local and peripheral signs of aortic insufficiency, splenomegaly, clubbed fingers and anemia: a blood culture was positive for an unidentified gram-negative organism, and slight signs of congestive cardiac failure, albuminuria and hematuria were present. There

was slight tenderness over the joints on palpation; otherwise the findings were unimportant. The anatomic diagnosis was: vegetative endocarditis of the aortic valves, jaundice, chronic passive congestion of the viscera, infarcts of the spleen and kidney, acute nephritis, focal suppurative meningitis and subacute synovitis.

The knee joints were opened and showed no excess fluid.

A microscopic examination of the synovia showed many papillary projections, some large with apparent reduplication of the synovial lining cells and some perivascular infiltration of lymphocytes; there were also masses of fibrin at points

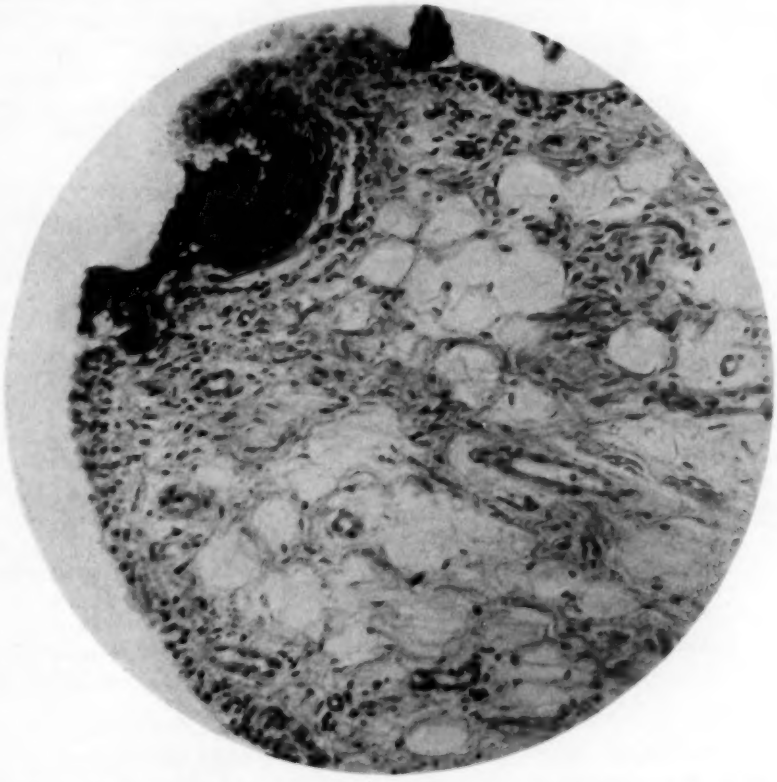


Fig. 8 (case 7).—Synovial membrane from a patient with subacute bacterial endocarditis, showing thickening of the synovia with small masses of fibrin on the surface. There is little reaction in the connective tissues (× 170).

on the surfaces of the projections. The fibrin looked fairly old in some areas, and leukocytes occurred in and around it. In a few projections some macrophages with blood pigment were present. In the synovial connective tissue there were scattered lymphocytes and a few mast cells. Other sections showed the same changes but to a much less marked degree.

The essential lesion was in the synovial connective tissue with perivascular infiltration of lymphocytes. The surface of the synovia was irregular in some areas and showed some masses of fibrin. On the whole, however, the surface cells were intact. The changes are shown in figures 8 and 9.

PNEUMOCOCCIC ARTHRITIS

CASE 8.—F. P., a white man, aged 52, was admitted to the hospital with pneumococcus type I lobar pneumonia of nine days' duration. The left knee joint had been fused ten years before on account of an arthritis of unknown cause. He was cyanotic and jaundiced. There were signs of solidification of the right lung and of peritonitis. The left elbow joint was swollen, painful and tender; when a needle was inserted into the cavity, pus containing pneumococcus type I was

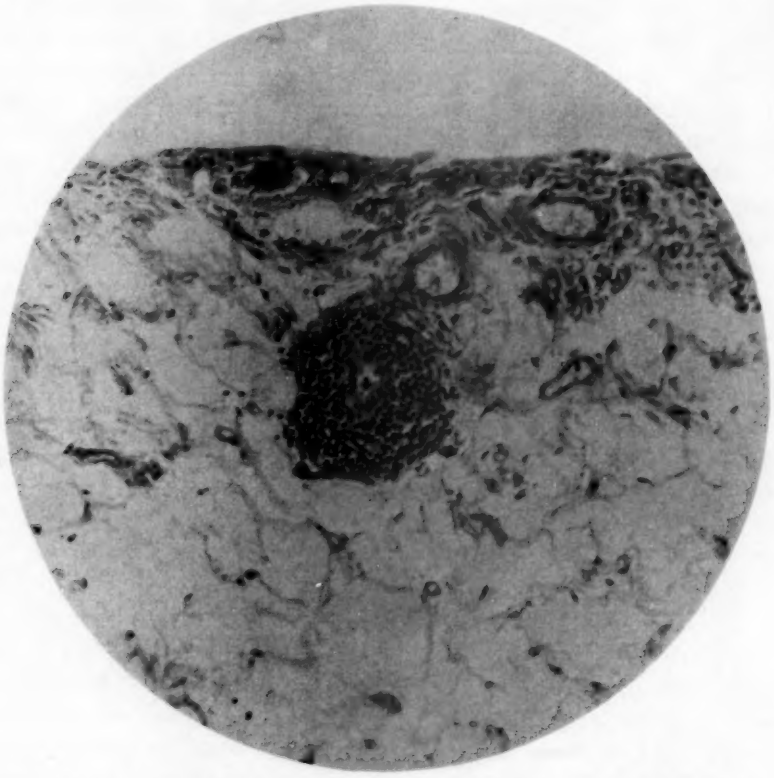


Fig. 9 (case 7).—Synovial membrane showing perivascular infiltration of lymphocytes. The patient had progressive subacute bacterial endocarditis with pains in the joints (× 170).

removed. The white blood cells numbered 16,200 per cubic millimeter. Death occurred on the tenth day of the disease. The clinical diagnosis was pneumococcus type I lobar pneumonia, pneumococcic arthritis of the left elbow joint and peritonitis. The autopsy confirmed this diagnosis.

On opening the left elbow joint it was found that the capsule was distended with pus. The entire articular surface of the humerus was completely denuded of cartilage and appeared irregular and granular. The synovial membrane was injected, thickened and covered with a fibrinopurulent exudate. At the edges of the humerus it was adherent. The articular surface of the ulna was similar in

appearance to that of the humerus; that is, the cartilage was completely destroyed leaving the underlying bone exposed and covered with exudate. The head of the radius was irregular, and the cartilage was destroyed.

Microscopic examination of the synovial membrane from the elbow joint showed that the synovial lining was destroyed and the surface covered with débris, leukocytes and, in places, masses of gram-positive diplococci. In the synovial connective tissue there were numerous lymphocytes, some plasma cells and a number of foci containing many macrophages engorged with blood pigment. Scattered through the tissues in places were numerous gram-positive diplococci. Smaller blood vessels throughout showed swelling of the endothelium, often with a perivascular infiltration of lymphocytes and macrophages, sometimes with thrombosis. Three large vessels showed acute lesions consisting of necrosis of their walls with fibrin deposits and infiltration with numerous polymorphonuclear leukocytes and some macrophages.

For the most part, the articular cartilage was completely destroyed. In places it persisted as a thin layer, definitely necrotic. There was an occasional island of living cartilage, especially in the deeper layers.

At the articular surface, where the cartilage had been lost, the normal subchondral bony layer had also disappeared for the most part. In this region there were trabeculae of bone surrounded by pus. The trabeculae were narrowed and irregular, and were evidently undergoing solution. Nuclei were present in the greater part of this affected bone. Where the bone marrow still persisted, osteoclasts were attacking the bone. In the deeper portions of the epiphysis, the bone as a whole was unaffected in spite of the numerous abscesses in the marrow. In one area where the cartilage and subchondral bone persisted there was a depression in the line of the joint with thickening and distortion of the bony trabeculae.

Scattered throughout the marrow were numerous small abscesses in which numerous cocci could be seen. Apart from these abscesses there were some areas of connective tissue proliferation, sometimes infiltrated with lymphocytes. This was especially prominent in one area near the articular surface where there was a marked depression in the surface of the joint.

Both knee joints were examined. The left showed a complete bony fusion, the result of an operation done ten years before. Neither gross nor microscopic examination of the tissues of the right knee showed any abnormalities.

The sequence of events and the pathologic changes in the joints in pneumococcic arthritis when the lesion begins as a blood-borne metastasis is as follows: At first there is an intense inflammatory reaction of the synovial membrane, starting beneath the surface and extending into the cavity of the joint. This is soon followed by destruction of the overlying cartilage and, finally, of the bone.

In most of the reported cases of pneumococcic arthritis the disease has appeared during or following a pneumococcic sepsis, the most common being pneumococcic lobar pneumonia. The arthritis is more often monarticular than polyarticular; the large joints are involved more frequently than the smaller ones, and the lesion is almost invariably suppurative. Associated with the arthritis there may be other metastatic lesions such as meningitis or endocarditis. Their presence, of course, definitely changes the prognosis. It is well to remember that pneumococcic arthritis requires prompt action with drainage of the joint cavity.

COMMENT

From these eight cases, certain facts are obvious. Infections of the joints occur in one of three ways: (1) extension of an infection directly into the joint cavity from an infection or wound of the skin (case 4); (2) extension of an infection from the bone directly into the joint cavity (case 3); (3) infection of the joint cavity by way of the blood stream (cases 1, 2, 5, 6, 7 and 8). An appreciation of the mode of infection will aid in an understanding of the final picture. By far the most common is the hematogenous route. This is true regardless of the infective organism, and in the cases described this was true of the meningococcic, gonococcic and pneumococcic infections. In these infections the inflammation began in the synovial connective tissue and about the blood vessels, later spreading to the synovial cells on the surface. If the lesion progressed, the cartilage and underlying bone were attacked and destroyed. If, on the other hand, the infection spread to the joint cavity from an osteomyelitis, then there was considerable destruction of both bone and cartilage and secondary involvement of the synovia, the principal lesion in the latter being localized near the surface and spreading downward rather than by the mode of progression described for involvement of the synovia from a hematogenous process.

Aside from the mode of infection there are other factors determining the final pathologic state; these will not be discussed at this time, but require consideration. They are: the type of infecting organism, the effect of pressure, the character of the cellular reaction and the presence of antiferment substances in the synovial fluid.

SUMMARY

The pathologic lesions of eight cases of infective arthritis due to streptococcic, gonococcic, meningococcic and pneumococcic infections and to an unidentified gram-negative coccus are reported.

The character of the change varied with the mode of infection, which occurred in one of three ways: (1) by the blood stream; (2) by direct extension from an osteomyelitis; (3) by direct extension from the skin overlying the joint.

In the cases in which the infection of the joints occurred as a result of a hematogenous infection, the process began in the synovial connective tissue, with infiltration of polymorphonuclear, lymphoid and plasma cells about the blood vessels and between the strands of connective tissue. As the infection progressed, the synovial lining was destroyed and completely replaced by granulation tissue. Later the cartilage and bone were involved in the process and destroyed.

When the bone was involved primarily, the outstanding lesions were a destruction of bone and the overlying cartilage. The inflammation of the synovia showed a progression from the superficial to the deeper layers.

The changes were characteristic of an inflammatory process and could be readily distinguished from degeneration.

THROMBO-ANGIITIS OBLITERANS

DISTRIBUTION OF THE LESION IN THE VESSELS OF THE LEG

J. R. E. MORGAN, M.D.
J. J. MacKenzie Fellow in Pathology, University of Toronto
TORONTO, CANADA

Since Buerger,[1] in 1908, first described thrombo-angiitis obliterans as a definite clinical and pathologic entity, affecting the arteries of the extremities, many contributions have been made to the literature on this subject. Subsequent to this date Buerger,[2] Allen and Willius,[3] Lewis,[4] Taube,[5] McGregor and Simson,[6] and Telford and Stopford,[7] to mention only a few of the many writers, have described the disease in almost all the arteries of the body.

In 1909 Buerger [2a] presented the results of his studies on this disease in relation to the veins. He showed that both arteries and veins were involved in the disease process, and published a chart recording the different vessels of the leg which were affected. This publication, however, did not present the distribution of the lesion within any one vessel, and a review of the literature has failed to reveal the desired information.

One of the questions that arose was: How is the disease process distributed along the course of any one vessel and how is it disseminated through the various segments of the vascular system? With the hope of obtaining some additional information in respect to these points special care was taken in the preparation and examination of the material available.

MATERIAL AND METHOD

During the past year the vascular system of the lower extremities was available for examination in three cases. In case 1 the arteries and veins were dissected out immediately after operation (Gritti-Stokes) and fixed in solution of formaldehyde. Blocks were taken every centimeter along the course of the arteries and the microscopic sections stained with hematoxylin and eosin and by the phosphotungstic

1. Buerger, Leo: Am. J. M. Sc. **138**:576, 1908.

2. (*a*) Buerger, Leo: J. A. M. A. **52**:1319, 1909; (*b*) Am. J. M. Sc. **149**: 210, 1915; (*c*) The Circulatory Disturbances of the Extremities, Philadelphia, W. B. Saunders Company, 1929, p. 368. (*d*) Buerger, Leo, and Kaliski, D. J.: M. Rec. **78**:665, 1910.

3. Allen, E. V., and Willius, F. A.: Ann. Int. Med. **3**:35, 1929.

4. Lewis, Dean: Arch. Surg. **15**:613, 1927.

5. Taube, Norman: J. A. M. A. **96**:1469, 1931.

6. McGregor, A. L., and Simson, F. W.: Brit. J. Surg. **16**:539, 1929.

7. Telford, E. D., and Stopford, J. S. B.: Brit. M. J. **2**:1035, 1924.

acid methods. In the other two cases the legs were sent to the laboratory and, in order to preserve the normal length of vessels during fixation, were treated by the following method: The skin and subcutaneous tissues of the leg and foot were removed, and the muscle planes were laid open so that when the whole limb was immersed in solution of formaldehyde the vessels were fixed *in situ*. The arteries were then dissected out along with their venae comites, accompanying nerves and perivascular tissues. After observation of the external features of the gross material, blocks were removed at intervals of 1 cm. along the course of the vessels and their cut surfaces noted. From these blocks sections were taken for microscopic study and stained by the aforementioned methods.

REPORT OF CASES

CASE 1.—M. S., aged 32, a laborer, a moderate smoker, born in Canada of Jewish parentage, was first admitted to the hospital on Aug. 19, 1930, with a complaint of pain in the left foot of six months' duration, with swelling and discoloration for four months. Pain was relieved by rest and heat. The patient also stated that there had been a red superficial swelling along the course of the veins of the left leg. The left posterior tibial and dorsalis pedis arteries were not palpable. The leg was swollen, blanched on elevation and assumed a mottled purple coloration when dependent. A small area of superficial venous thrombosis was present. The left leg was cooler than the right.

A left lumbar sympathectomy was performed by Dr. D. W. G. Murray, and immediately following the operation the temperature of the left leg rose 4 C. For about one year after discharge the patient was free from symptoms; then he began having recurrence of pain on exercise of the left limb. The increased warmth of the leg gradually decreased so that at the time of readmission, on July 14, 1932, it was again cooler than the right. There was a small gangrenous ulcer between the second and third toes and extending a short distance over the dorsum of the foot. A faint pulsation was felt in the dorsalis pedis artery, but the posterior tibial artery was not palpable. Several firm, cordlike structures were felt along the course of the superficial veins.

Following failure of the ulcer to heal the leg was amputated (Gritti-Stokes) on Aug. 10, 1932.

CASE 2.—C. K., aged 31, a brakeman and a moderate smoker, born in Canada of British parentage, was first admitted to the hospital on March 7, 1932, complaining of pain in the feet and calves. This disability was brought on by exertion and had gradually increased in severity for two years. At first the pain was present only after a full day's work, but at the time of admission it was felt shortly after rising. The pain was relieved by rest and heat. Seven months before admission the patient suffered an abrasion of the left great toe; this ulcerated and would not heal. On examination both feet were reddened and cool. The feet blanched when elevated and became cyanosed when lowered. A small area of ulceration was present on the dorsum of the left great toe with marked tenderness of the tip of this toe. The ulcer failed to heal in two months of general supportive treatment, and a left lumbar sympathectomy was performed, following which there was a good rise in the cutaneous temperature of the left limb. The ulcer healed; the patient was able to walk farther, and the foot was more comfortable.

The patient was readmitted two months later with the ulcer again present. There was also an increasing disability of the feet and legs, with progressive

diminution of exercise tolerance before the onset of pain. At this time the left great toe was amputated with slow but good healing of the stump.

Five months after discharge the patient returned to the hospital with the complaint of increasing pain in the right leg and foot so that his walking limit was reduced to 200 yards (182.8 meters). On examination the right leg was cooler and of a deeper color than the left, and the dorsalis pedis and posterior tibial arteries were not palpable. A right lumbar sympathectomy was performed by Dr. D. W. G. Murray, following which there were increased heat, comfort and exercise tolerance of the limb. The patient again returned to the hospital on June 21, 1932, with a small nonhealing ulcer at the site of the amputation. There was no pain in either calf; exercise tolerance was increased, and none of the peripheral vessels were palpable. The ulcer healed very slowly.

Following discharge the ulcer again broke down and became gangrenous. All methods of treatment proved unsuccessful. A Gritti-Stokes amputation of the left leg was performed on Feb. 22, 1933.

CASE 3.—R. H., aged 47, a gardener and a moderate smoker, born in Canada of British parentage, was admitted to the hospital on May 3, 1933. Two years previously he began to have pain and numbness in the left hand, beginning in the left index finger. The pain became progressively worse, and the hand and arm became cold and waxen. Three months after the onset of the symptoms a cervical sympathectomy was performed by Dr. D. E. Robertson. Following the operation there was relief of pain, with increased warmth of the arm and hand.

Eighteen months before admission to the hospital pain appeared in the right foot; this was soon followed by swelling. During the eight months previous to admission almost the entire dorsum of the foot became ulcerated and gangrenous. The patient was unable to walk or use his arms and hands without suffering from cramplike pains.

On examination the left radial artery was not palpable. The left foot and leg were swollen and edematous, with large sloughing gangrenous ulcers covering almost the entire dorsal surface of the foot. No vessels were palpable in the left leg.

On May 4, 1933, Dr. R. I. Harris performed a Gritti-Stokes amputation, with good healing of the stump.

PATHOLOGIC CHANGES

Although both the gross and the microscopic morbid anatomic changes of thrombo-angiitis are well known, it is not amiss to state briefly the salient points of these observations. Of the various methods of recording the results of these histologic studies a classification which divides the disease process into acute and chronic stages has been chosen. This has been done although it is realized that the lesion begins as an acute process and later progresses to the chronic stage and that all gradations between these extremes may be observed. It is believed, since the great majority of all the sections studied fall within either of these groups, that this classification is the most useful. The following is a brief description of the lesions as seen in the gross and microscopic examination of the available material.

Gross Appearance.—The three cases presented a marked similarity in the gross appearance of the vascular tissues. In many regions the periarterial fibrous connective tissue was greatly increased in amount and formed a firm, cordlike structure which also contained the immediately adjacent veins and nerves. The cross-section of these areas showed the lumen of the artery to be filled with a yellowish-gray, firm tissue which, when the vessel was gently milked, revealed many fine canaliculi through which sanguineous fluid escaped. The remaining perivascular fibrous tissue presented little or no increase in amount, and the artery, veins and nerves could be easily separated. The cut surface of most of the latter areas revealed

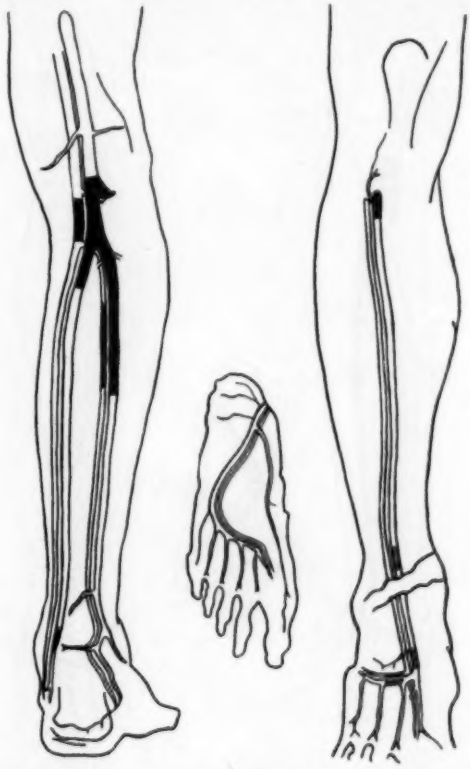


Fig. 1 (case 1).—Distribution of the chronic (solid black) and acute (barred) lesions seen in the vessels of the leg in thrombo-angiitis obliterans.

shrunken vessels with patent lumens, although in an occasional section the lumen was filled with a soft reddish-brown mass of fresh thrombus. Thus it was noted, that where the chronic arterial lesion was present the perivascular fibrous tissue was firm, tough and markedly increased in amount, while little or no change was observed about the acute lesion. Occlusion of the veins occurred with less frequency, and when present was usually associated with arterial thrombosis.

Histopathologic Changes.—Acute Stage: In this phase of the disease process there was evidence of an acute inflammatory reaction involving all the coats of the vessel. The lumen was filled with a fresh red clot, throughout which, especially in its periphery, there were small collections of leukocytes. The cellular infiltra-

tion of the adventitia and perivascular tissue was chiefly of the polymorphonuclear variety, and these cells were concentrated about the small arterioles and venules; at times the reaction was granulomatous. The pathologic changes seen in the veins were similar to those observed in the arteries. The acute lesions of both artery and vein occupied but short segments of the vessels, and when present, were only 1 or, more rarely, 2 cm. in length. It was also noted that in the acute lesions of the veins, in which the histologic structures were still discernible, the formation of a thrombus was usually in relation to the valvular cusps.

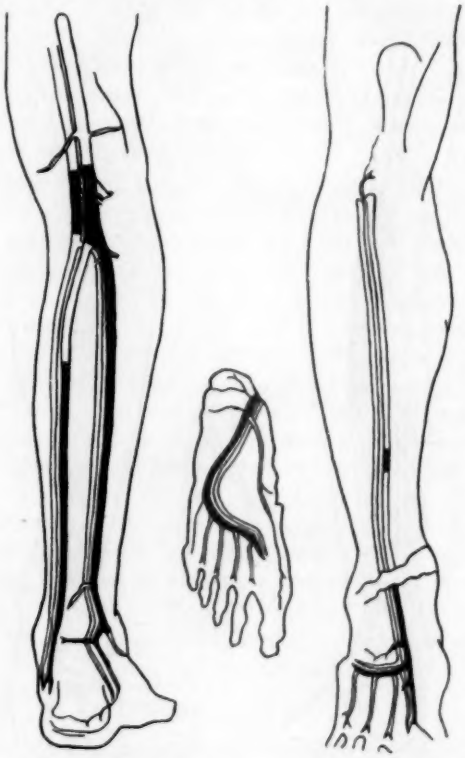


Fig. 2 (case 2).—Distribution of the chronic (solid black) lesions seen in the vessels of the leg in thrombo-angiitis obliterans. No acute lesions were present in this case.

Chronic Stage: Vessels showing this lesion presented the typical picture of recanalization of an organized blood clot with blood sinuses irregularly coursing through it. In this organized thrombus, especially about the sinuses, were many inflammatory cells, chiefly lymphocytes with a few polymorphonuclear leukocytes and endothelial cells. A few lymphocytes and polymorphonuclear leukocytes were scattered through the media of most of the involved areas and especially about the vasa vasorum. The perivascular tissue consisted of moderately dense fibrous tissue surrounding the artery, veins and nerves, with many leukocytes scattered throughout. The venae comites, when affected by the chronic stage of the disease, presented a picture quite similar to that described.

Distribution in the Vessels of the Leg.—On microscopic examination sections from each preparation showed one artery and two or more veins. Since it was obviously impossible to chart all these vessels, only the larger of the venae comites was described. In many cases, however, the condition of one or more of the smaller vessels differed markedly from that of the one recorded. For example, though the larger vein contained an old chronic obturating mass, the other vessel or vessels were patent, or filled with a fresh red thrombus, or contained a type of lesion similar to that of the larger vein. Charts 1, 2, and 3 give a diagrammatic representation of the distribution of the lesions found in the three cases.

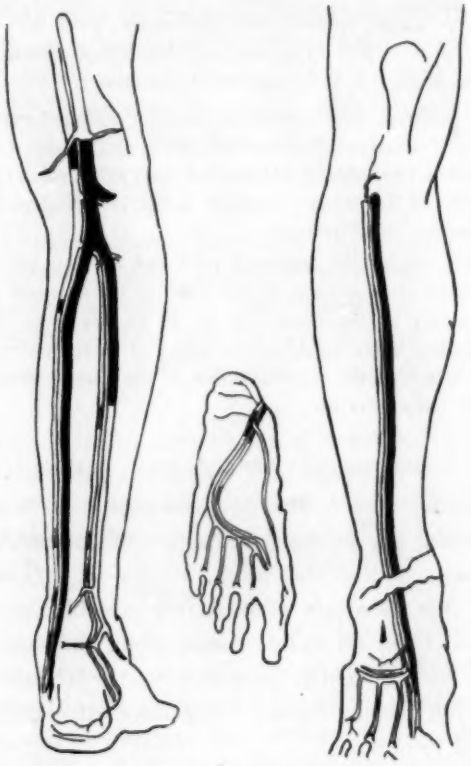


Fig. 3 (case 3).—Distribution of the chronic (solid black) and acute (barred) lesions seen in the vessels of the leg in thrombo-angiitis obliterans.

Case 1: The lumens of the lower portion of the popliteal, proximal 4 cm. of each of the anterior and posterior tibial, and upper half of the peroneal arteries were filled with masses of recanalized fibrous tissue (chart 1).

No other chronic arterial lesion was found except a small area in the posterior tibial artery at the level of the ankle joint. There were small patches of recent red thrombi in the distal part of the anterior tibial artery and in the midportions of the dorsalis pedis and arcuate arteries. Except for these regions the arteries presented little evidence of pathologic change.

The distal two thirds of the upper half of the peroneal and the lower portion of the popliteal vein were sites of the chronic stage of the disease. The only

locus of fresh thrombosis and active reaction in the veins of this leg was one small patch opposite a similar lesion in the arcuate artery.

Case 2: In this leg the popliteal, peroneal, dorsalis pedis, arcuate, distal three fourths of the posterior tibial and plantar branch of the posterior tibial arteries were all occluded by recanalized fibrous tissue typical of the chronic stage of thrombo-angiitis obliterans (chart 2). The proximal quarter of the posterior tibial and the whole extent of the anterior tibial arteries were patent, except for a small area of old thrombus formation in the upper portion of the distal third of the latter.

There were no acute lesions, and the veins were all patent except the popliteal, which was occluded by a plug of recanalized fibrous tissue having the typical appearance of the chronic stage of this disease.

Case 3: The popliteal, posterior tibial, anterior tibial, dorsalis pedis and upper half of the peroneal arteries all presented the typical appearance of the chronic lesion (chart 3). The remaining portions of the main arteries were clear, except for a small area of old thrombus formation in the proximal portion of the plantar branch of the posterior tibial artery.

The proximal 4 cm. of the popliteal vein and a small patch in the posterior tibial vein presented lesions similar to that seen in the adjacent arteries.

The venae comites of the distal halves of the posterior tibial and peroneal arteries each contained three small patchy areas of recent red thrombus and there were two similar lesions in the veins adjacent to the plantar branch of the posterior tibial and dorsalis pedis arteries.

DISSEMINATION OF THE LESION

The sections were examined microscopically with a view to determining, if possible, any evidence indicative of the method of spread of the disease process within the vessels of the leg. The results of this study revealed that there are at least two possible procedures: (1) by direct extension, from an initial focus, along the vessel wall; (2) by multiple acute lesions which progress to the chronic stage without spreading, the intervening spaces being later attacked by other irregularly distributed lesions.

In case 1 the most distal portion of the thrombus in the peroneal artery appeared to be the oldest lesion. At this site the occluding mass consisted of dense, mature fibrous tissue which was well canalized and contained relatively few lymphocytes. The thrombus formation in the more proximal sections consisted of progressively less mature fibrous tissue and a heavier infiltration of leukocytes. This immature type of thrombus formation filled the popliteal artery and extended into the anterior and posterior tibial vessels. From these observations it appeared as though the lesion had begun in the lower portion of the proximal half of the peroneal artery and extended upward into the popliteal artery.

In the other two cases the lesions in these vessels were of a more mature type, and the gradation from recent to old was not so apparent. Since the vessels in only three cases were examined it is difficult to draw any conclusions, although the constancy of this type of lesion, in these particular vessels, appears to be of significance. These observations, however, are strongly suggestive that the disease process begins in one region and spreads from that point.

Each of the three cases presented at least one small isolated area showing the chronic type of lesion. These observations suggest that a small patch of the acute lesion may progress to the chronic stage without spreading either proximally or distally. It is probable that as the disease progresses the intervening spaces are occupied by other irregularly distributed areas of acute thrombus formation which in their turn become chronic. This process may continue until all, or nearly all, of a vessel is occluded by the chronic lesion.

These observations suggest that either of the aforementioned two methods of dissemination of the lesion may take place within the vessels. Since case 1 presented evidence of direct spread, as described, and also patchy areas of both the acute and the chronic stage, it is probable that both types of dissemination of the disease process are present in the same case.

There is no evidence to support the theory that the primary lesion is one involving the smaller vessels of the periphery with extension from this point. Indeed, the reverse is probably true, for the gangrene of the toe in case 1 clearly antedated the acute lesions found in the vessels of the foot.

SUMMARY

The entire course of the vessels of the leg was examined in three cases in which a clinical and pathologic diagnosis of thrombo-angiitis obliterans was made. The three cases presented a duration of eighteen months or more, and amputation was performed only after other methods of treatment had failed. Only one of the three patients was of Jewish origin.

No one portion of an artery was unaffected in all three cases. The popliteal artery and the upper half of the peroneal artery, which were occluded by an old recanalized thrombus, were the only vessels showing a constant lesion in all three instances. A similar type of lesion involved the popliteal veins and represented the only constant localization of the lesion in the veins. The only example of (recent) thrombus formation in the arteries was found in case 1, and only one of the adjacent veins showed a similar lesion, the remainder being freely patent. In case 3 some of the venae comites contained patchy areas of acute red thrombus.

About one half of these areas were adjacent to arteries showing the chronic stage of the disease while the others were found beside arteries with little or no pathologic change.

CONCLUSIONS

The lesions in thrombo-angiitis obliterans may be present in any portion of any of the larger arteries or veins of the leg, though they are much more common in the arteries.

The popliteal artery, the proximal half of the peroneal artery and the popliteal vein were the only constant sites of the disease process.

The lesion may originate in any part of any artery with or without involvement of its adjacent venae comites or it may begin in any part of a vein without a similar condition being present in the immediately adjacent artery.

The lesion commences in one or more small isolated areas and later progresses to the chronic stage. The pathologic process may spread from one or more of these foci, or the intervening spaces may be occupied by irregularly scattered lesions of a similar type.

GENERALIZED TORULOSIS ASSOCIATED WITH HODGKIN'S DISEASE

MARION S. FITCHETT, M.D.
NORFOLK, VA.
AND
FRED D. WEIDMAN, M.D.
PHILADELPHIA

In a recent monograph Freeman [1] was able to collect only forty-four instances of cerebrospinal torulosis. Generalization occurred in but three cases to which Weidman and Ratcliffe [2] have added an instance of extensive involvement in a chetah dying in captivity in the Philadelphia Zoological Garden. In addition to the widespread visceral involvement, the case here reported disclosed massive hyperplasia of tissue (lymph nodes?) which has never been approached in previously described cases in man, although the involvement in the chetah compared favorably with it in several respects. This report is submitted primarily, therefore, because (1) it is the fourth case with widespread visceral involvement and (2) Hodgkin's disease was associated with the torulosis (yeast cells were present in great abundance in masses of lymph nodes affected by Hodgkin's disease). It might be added that (3) the involvement of the mesenteric and mediastinal lymph nodes was so outstanding that attention must be attracted to some other portal of entry of the disease than the cerebrospinal system. The latter is commonly the only system in which the micro-organisms can be demonstrated, in which case the nasal passages are regarded as the portal of entry.

REPORT OF A CASE

History.—A Negro, 18 years of age, was admitted to St. Vincent's hospital in Norfolk, Va., May 7, 1931, and died thirteen days later. He had been healthy up to three years previously, at which time the disease made its first appearance in the left axilla in the form of "hard, round lumps." Similar lesions then developed in the other axilla, the neck and both groins. They were not tender or suppurative. One year previous to admission an irritating and nonproductive cough developed, which persisted. Three months previously the face became swollen, the swelling extending down the neck on both sides. At this time dizziness and headache became so severe as finally to make the patient take to bed. In the last few days he was delirious.

From the Laboratory of Dermatological Research, University of Pennsylvania.

1. Freeman, W.: J. f. Psychol. u. Neurol. **43**:236, 1931.
2. Weidman, F. D., and Ratcliffe, H. L.: Arch. Path., to be published.

Physical Examination.—This showed a greatly emaciated Negro youth with marked swelling of the face, head and neck. Questions were answered rationally, but the patient was very hard of hearing. The eyes were prominent, and both lids were swollen. The pupils were dilated and reacted sluggishly. Both disks were hazy and had engorged veins. The patient was almost totally blind, being able to see only a bright light. The ear drums appeared normal, yet hearing was reduced to that of a very loud conversational voice. There was marked congestion of the mucous membranes of the nose and throat. The neck was stiff. Lymph nodes in the neck were enlarged, varying in size up to that of a walnut. They were hard, discrete and movable, but were not tender.

The swelling of the neck did not appear to extend below the clavicles. The veins over the wall of the chest were dilated. Retrosternal dulness extended beyond normal limits on both sides. The heart appeared to be normal, and no abnormal physical signs could be elicited with respect to the lungs, except that the breath sounds were intensified. There were several enlarged lymph nodes in both axillae, one of which was as large as a hen's egg; otherwise, they presented the same physical characteristics as those in the neck.

The abdomen was scaphoid. The spleen was barely palpable. The liver was not enlarged. Many enlarged lymph nodes were present in the groins. There was no edema of the legs. Small lymph nodes could be felt in the epitrochlear and popliteal spaces.

The knee jerks were exaggerated, and there was a positive Kernig sign.

Laboratory Examination.—Nothing abnormal was found in the urine except a moderate amount of albumin.

The erythrocytes numbered 3,800,000, with 16,000 polymorphonuclears. The hemoglobin was 70 per cent. In the differential count there were 97 per cent polymorphonuclears, 2 per cent lymphocytes and 1 per cent eosinophils. Blood cultures were sterile on two occasions. The Wassermann and Kahn reactions of the blood were negative.

The spinal fluid was turbid and contained no globulin. Twenty-five milligrams of dextrose was found in one hundred cubic centimeters. The sediment contained many yeast cells, and occasionally a polymorphonuclear cell was noted. The Wassermann and Kahn tests gave negative results. Pure culture of a yeast organism was secured.

A node was removed from the left axilla for biopsy; scrapings from its cut surface disclosed many yeast cells. In histologic sections, however, they could not be recognized. We agree with Dr. Roache that the changes were suggestive of Hodgkin's disease, and, indeed, we should go considerably farther. The normal architecture of the node was completely obliterated by closely packed masses of lymphocytes. At scattered intervals Dorothy Reed cells were readily identifiable, and in places there were definite overgrowths of fibrous tissue. Eosinophils, however, were not found. In certain areas endothelial cells occurred, which were similar to those which will be described later in materials from necropsy and in an experiment on a cat, but which were never as conspicuous.

Autopsy (Mary E. Roache).—The body was that of a mulatto youth, apparently 18 years of age, highly emaciated, weighing about 65 pounds (29.5 Kg.). Rigor was absent. The intercostal spaces were sunken, the wrists prominent and the abdomen scaphoid. There was moderate enlargement of superficial cervical and axillary lymph nodes. The inguinal lymph nodes were much enlarged. Small, superficial, freely movable nodules were palpated under the skin of the arm, abdomen and lower extremities. Decubitus was present over the sacrum.

The dura was much congested and apparently thickened. The pia mater was likewise congested and exhibited areas of grayish exudate around the blood vessels, especially at the base, where the optic nerves, medulla and pons were covered in addition by thick yellowish fluid. Fluid collected from the posterior fossa contained many yeast cells, pus and other degenerated cells. The brain showed many small punctate hemorrhages through both the gray and the white matter. The medulla revealed hemorrhagic lines and minute punctate hemorrhages. Neither abscesses nor areas of softening were observed. On examination with a hand lens after fixation in formaldehyde, extremely minute cysts could be observed in the cortex of the cerebrum.

Subcutaneous fat was absent from the abdominal wall. The abdominal muscles were wasted. There was no fluid in the peritoneal cavity.

Along the mesenteric attachment of the small and large intestines were nodules from 1 to 3 cm. in diameter. In the mesentery itself there were similar masses measuring up to 9 cm. in diameter. Enlarged nodes could be felt behind the peritoneum.

The spleen was about three times the normal size. Its surface was grayish and had a thickened capsule containing two dense, firm scars. The latter, on section, were yellow, firm and fibrous. Nothing notable was observed on the surface of the section. It appeared to be infiltrated by connective tissue. The liver extended to the edge of the costal margin. It was dark red, firm and without gross lesions. The kidneys were enlarged and soft. The capsule was adherent, the surface of the kidney being torn and granular after removing the capsule. On the surface of the section the renal tissue was orange-yellow and mottled with hemorrhagic lines and dots. The pancreas was soft and flaccid. There were several nodules from 2 to 4 cm. in diameter in its head. The cut surface was pink, translucent and firm. The urinary bladder presented a few small nodules on its surface.

Covering the precordium was a wedge-shaped mass infiltrating both the pericardium and the pleura on either side. When sectioned, it measured 6 cm. in thickness; it was soft and appeared to be composed of dark red granulation tissue, with caseation and softening in the center. Direct examination of smears revealed large yeast cells and degenerated tissue cells.

The heart was moderately enlarged. The musculature did not contain nodules, nor were there any adhesions. The lungs were flaccid and partly collapsed, containing little air. Hard, enlarged lymph nodes surrounded the hilus of each lung, and similar nodules were observed under the pleura.

Histologic Examination.—Sections from the lungs, kidneys, spleen, lymph nodes, pancreas, cerebrum, cerebellum and spinal cord were embedded in paraffin and examined histologically.

Lungs: In places the walls of alveoli were irregularly fibrosed; in some regions air spaces were collapsed. At no place was there any inflammatory infiltration. Yeast cells could not be observed. The bronchi appeared normal.

Kidneys: The capsule appeared normal. The interstitial tissue was not increased, except in foci which will be described. The blood vessels were injected. The tubular epithelium was coarsely granular and swollen, leading to extensive occlusion of the lumens. The glomerular tufts were normal, except when affected by yeast cells, as will be noted.

Torular Features: These were extensive. Torula cells were observed (1) within glomerular tufts, (2) within kidney tubules and (3) in small granulomas,

which affected both the interstitial and the tubular tissue. All these changes affected the cortex almost to the exclusion of the medulla.

The glomerular tufts were frequently eight or ten times normal size, in which case they were scarcely recognizable as glomeruli. They became transformed into multilocular cysts as the result of proliferation of the fungus cells in the lumens of the capillaries, but there could not be any doubt as to such an origin

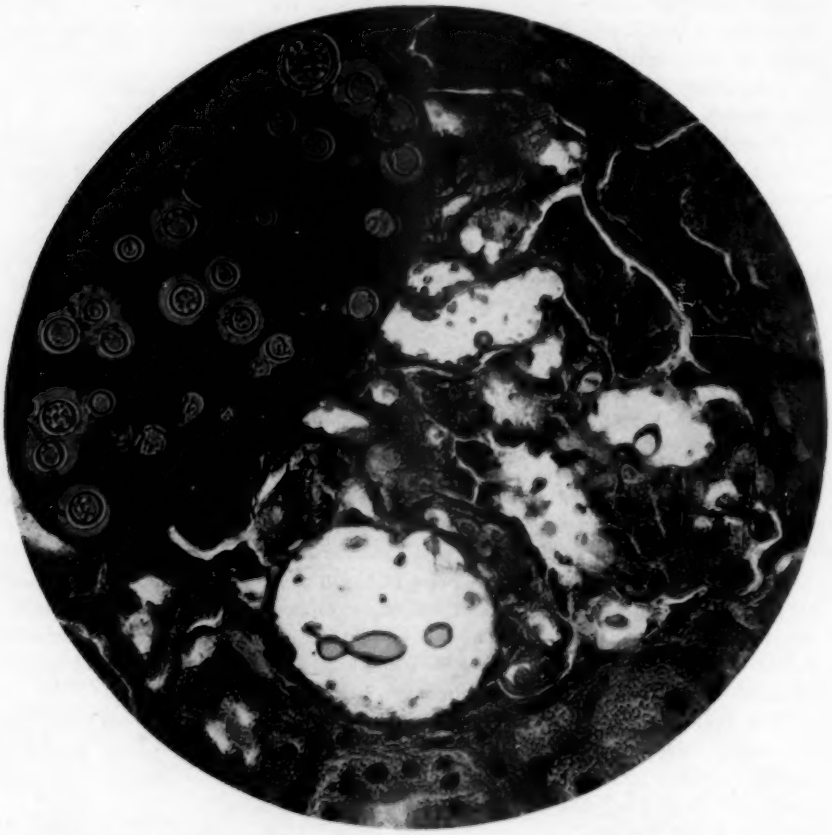


Fig. 1.—Torula cells in the capillary lumens of a glomerular tuft of the kidney; the black insert shows torula cells in culture and demonstrates the mucinoid envelop (wet india ink preparation).

of the cysts on examining smaller glomeruli in which the process was beginning. Only a small part of the contents of the cysts was comprised of the yeast cells themselves; between them were granules and minute hyaloid globules. The precise nature of the latter could not be stated with finality, i. e., whether they originated in torula cells or in degenerated tissue, but we favor the latter origin and believe that they were analogous to the "exudative" hyalin seen in glomeruli in some of the exanthems. None of the granules inclined to a bluish tint such as would indicate that the mucinoid substance observed in the interior of torular cysts at necropsy was true mucin. The yeast cells varied widely in size: smaller

ones were almost coccoid, while larger ones were larger than red blood cells. Many of the cells were budding. There was no cellular infiltration around the glomeruli.

When affecting the renal tubules, fungus cells were observed in the lumen intermixed with more or less disintegrated lining epithelial cells. In this location the lesion did not take the form of a cyst. For the most part, inflammatory reaction was absent around these foci also, but some large lymphoid cells were clustered at the margin of an affected tubule here and there. In no case, however, was such a lesion entirely invested by the infiltrate.

The third type of lesion, the granuloma, consisted mainly of small masses of yeast cells intermixed with degenerate cytoplasmic granules and nuclei of round cells, but the nuclei were not fragmented or associated with polymorphonuclears. Peripherally, the reactive cells tended to take the form of endothelioid cells, and at places the nuclei became clustered in such a way as to suggest giant cells. However, true Langhans forms were never observed, nor was there any definite lymphocytic infiltration or necrosis.

Pancreas: The interlobular fibrous tissue was slightly thickened and of old adult type. The parenchymal cells were apparently normal. The acini were poorly outlined, leading to the suggestion that they were fused (autolysis?). The islands of Langerhans were numerous, well formed and of normal size; collections of yeast cells were observed in but few. There was some budding. A solitary focus of yeast cells was also observed within one of the lobules. In neither case was there any tissue reaction around these lesions.

Spleen: There was no fibrosis of the capsule, but the trabeculae were thickened and deformed. The reticulum was also extremely thickened, particularly in the splenic nodules, where a comparatively coarse network invariably traversed them, and in places the endothelium of the sinuses had proliferated to the degree that it formed a continuous epithelium-like lining. The central arteriole could scarcely be made out, if at all. Still, the general architecture of the organ was well maintained. Lymphocytes were conspicuously scarce in the splenic pulp, but red blood cells were fairly numerous. By contrast, large monocytes suggestive of the mononuclear examples of Dorothy Reed cells were conspicuous and numerous in the sinuses, but their outlines were not sharp, and the cytoplasm was loose as though it were edematous. In addition to such hyperplastic tendencies, clusters of small (rarely larger) foreign body giant cells appeared around some minute islands of granular, almost hyaloid substance which suggested a focus either of edema or of a similar hyaloid substance. The end-result was an ill-defined granuloma unassociated with endothelioid cells, but which consisted almost entirely of the giant cells. Torula cells appeared within their cytoplasms rather frequently; more rarely they appeared independently in the centers of the granulomas. A further abnormality consisted in minute clusters of polymorphonuclears distributed numerously but at wide distances throughout the section. Eosinophils were not observed.

Yeast cells were observed in, and adjacent to, the giant cells just described and also in the lumen of smaller vessels. The inconspicuousness of central arterioles of the splenic nodules is thus perhaps explained; i. e., it is due to mycotic thrombosis at some preceding date. The coarsely granular, bronze-black pigment present in goodly quantities in the interior of the yeast cells recalled that of malaria. (Incidentally, similar grains of pigment were observed within some of the yeast cells in the pancreas.) We do not believe, however, that this was malarial pigment, as we have observed it in other cases of torulosis, including

experimental cases in rats. It is probably a product of the yeast cell itself, but may represent phagocytosed blood pigment.

The end-result of the changes just described was a definitely, uniformly and diffusely fibrosed splenic pulp, poor in lymphocytes but rich in hyperplastic endothelium and interspersed with minute granulomas comprised of small, poorly formed giant cells of the foreign body type. The picture was not quite that of Hodgkin's disease, even eliminating the granulomas. Yeast cells were not numerous, but were readily observed when searched for.

Peribronchial Lymph Nodes: The architecture of this organ was almost lost; its identification rested largely on the great quantity of anthracotic pigment in the fibrous parts. Only in places were there any traces of sinuses or cortical follicles. The section consisted mostly of fibrous tissue, which appeared largely as dense hyaline masses, but also as strands which infiltrated the lymphadenoid

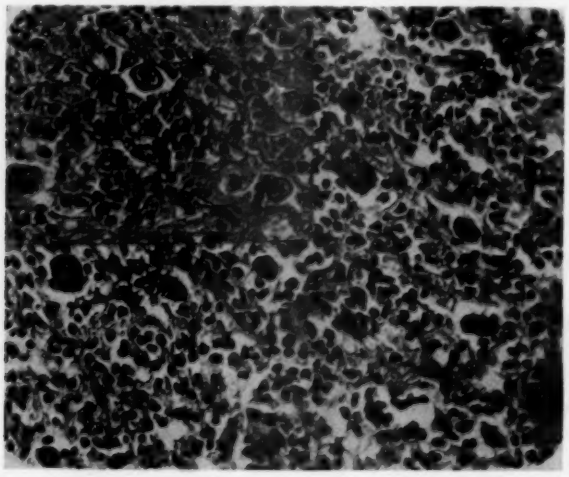


Fig. 2.—Section of the peribronchial lymph nodes; the spleen showed an identical type of change, as illustrated in the insert.

regions more or less coarsely. Elsewhere the tissue was comprised of a fibrous reticulum, which was delicate in some places and very coarse and hyaline in others. The cells within its meshes were largely lymphocytes. There were moderate numbers of endothelial cells in certain small restricted areas, but they were decidedly inconspicuous by comparison with the outspoken endothelial hyperplasia which preponderated in the mediastinal mass next to be described. Dorothy Reed cells, mostly mononuclear, but frequently classically multinucleate and with indented nuclei, were abundant. There was a rich network of blood vessels throughout, many of which were hugely dilated. Eosinophils and torula cells were not recognized.

Mediastinal Mass, Section 1: The changes here were of the same order as those in the peribronchial lymph node, except that the fibrosis was more extreme and the endothelial features had increased sufficiently to equal the lymphocytic ones. The Dorothy Reed cells were largely located in the more fibrous parts, much less frequently in the reticulo-endothelial ones.

Section 2: The architecture of the lymph node was scarcely recognizable; at most, only an occasional lymph sinus could be identified. Lymphocytes were scarce; when present, they were scattered loosely on the reticulum and in the sinuses. Otherwise, most of the section consisted of dense fibrous trabeculae or even expansive areas which communicated with narrower strands which represented the thickened reticulum normal in the organ. Other and extensive portions of the tissue consisted of a delicate reticulum which was not arranged according to the normal architecture of a lymph node with its sinuses, but simply as a diffusely interlacing network. On such a network great numbers of endothelial cells with broad, more or less stellate cytoplasms were observed. They were indefinitely outlined, and the cytoplasms had a rarefied appearance indicative of edema or some kindred retrogressive change. Lymphocytes were intermixed rather sparingly. In addition, other cells were abundantly present which approached decidedly the form of the Dorothy Reed cell or even attained its

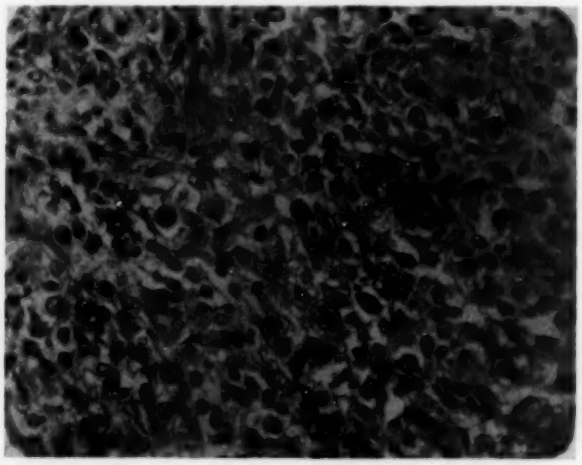


Fig. 3.—Section of the mediastinal mass, showing changes of the order of malignant lymphoblastoma.

classic form. Their cytoplasms were scanty and had frayed-out margins, and the nuclei were almost gigantic. The latter were ovoid, rich in chromatin and frequently indented. At times there were two or three such nuclei in a single cell. Capillary blood vessels were not numerous, but larger blood vessels (of venous type) were plentiful and distended. Neither eosinophils nor yeast cells were observed. Several smaller or larger areas of necrosis occurred in which the nuclei no longer took the basic stain, yet in which the general architecture just described could still be made out. Indeed, in such necrotic areas one could still identify both the older, fibrous and the younger, hyperplastic phases of the general tissue change, indicating that the necrosis was indiscriminate, involving not only the older, fibrous but also the younger, more cellular parts.

Definitely circumscribed granulomas which might be interpreted as tuberculous were not observed. However, regions of beginning necrosis were sometimes present, within which fibroblasts had become deformed in such a way as to resemble endothelioid cells, but the additional histologic criteria of tuberculosis were not present.

Section 3: In this sample of material there were none of the larger areas of hyaloid fibrous tissue, except in the thickened capsule. The latter contained, in addition, several lobules of highly degenerate, swollen skeletal muscle fibers. The nuclei of the latter were frequently of gigantic vesicular character, and their cytoplasms were highly rarefied, as though by edema. In places the edema was so extreme that in transverse section the lobule of muscular tissue might be mistaken for a lobule of fatty areolar tissue. Incidentally, there were regions deeper down in the main portions of the mediastinal mass where such cells had become enclosed and dissociated by the reticulo-endothelial cells to the extent that they became difficult to identify as muscle cells. In such position they appeared as foam cells, not so much of the xanthomatous type as of the Gaucher type. In any event, their position deep in the mediastinal mass would serve to indicate the infiltrative character of the mass, i. e., it was sufficiently extensive to enclose portions of skeletal muscle.

In this specimen also the main body of the mass consisted of a fibrous reticulum which, however, was not nearly so dense as that of the other members of the reticulo-endothelial system which have been described previously. Capillaries, however, were abundantly present on the reticulum. The cells were preponderantly endothelial (Dorothy Reed cells are included under this heading), although there were a few minor concentrations of lymphocytes in various portions of the section. Eosinophils or torula cells were not recognized, although the latter were definitely identified on direct smear made at the time of autopsy. The marked vascularity, the infiltrative character in the periphery and the large size of the nuclei of the cells in this position prompted thoughts of sarcoma. However, the adherence of most of the cells to an endothelial type and the coarseness of the reticulum prevented such a conclusion in our opinion, unless so-called Hodgkin's sarcoma be admitted to the category of the sarcoma. With such destruction of normal architecture and such a degree of hyperplasia and infiltration, the reactive processes were of an activity far surpassing any ordinary hyperplastic lymphadenitis.

Brain: Even with the loupe, minute cysts were made out in the cortex; under the microscope they were observed to be rather sharply outlined and solidly filled with yeast cells similar to those already described in the kidney. Here, too, there was no surrounding inflammatory reaction; at most, a few endothelioid cells could be discovered at the lining of the cyst. The cysts occurred far more abundantly in the sulci than over the free surface of the convolutions. Most of them were elongated, the long dimension being directed perpendicularly to the pia mater; as a blood vessel could almost invariably be distinguished in each cyst, it was obvious that the cyst had had its beginning around the blood vessels. It is notable that the nerve tissue around the cysts did not exhibit any signs of degeneration; the margins of the cysts had an almost punched-out appearance. In the meninges the fibrillar stroma had become almost entirely replaced by masses of closely packed yeast cells, within which the outlines of the arteries could still be made out.

The yeast cells occurred both free in tissue spaces and within large swollen phagocytic cells; in some cases dozens of yeast cells were packed within a single phagocyte. They were exceedingly small when compared with those seen in the kidney and spleen, and were distorted beyond recognition, probably from overfixation. Budding or pigmentary forms could scarcely be observed. There was always a wide halo around each cell, representative of its mucinoid capsule.

Cerebellum: The meninges were thickened by enormous numbers of yeast cells, each with its halo. There were no cellular reactions against them. In only one or two of the numerous sections studied were cysts found; singularly, they were confined to the medulla.

Spinal Cord: Yeast cells were confined to the meninges. The bronze-black, spherical grains of pigment which have been alluded to were abundant both intercellularly and within phagocytes. One or two granulomas were found in the spinal cord itself; they consisted almost exclusively of endothelioid cells. Torula cells were not observed in them.

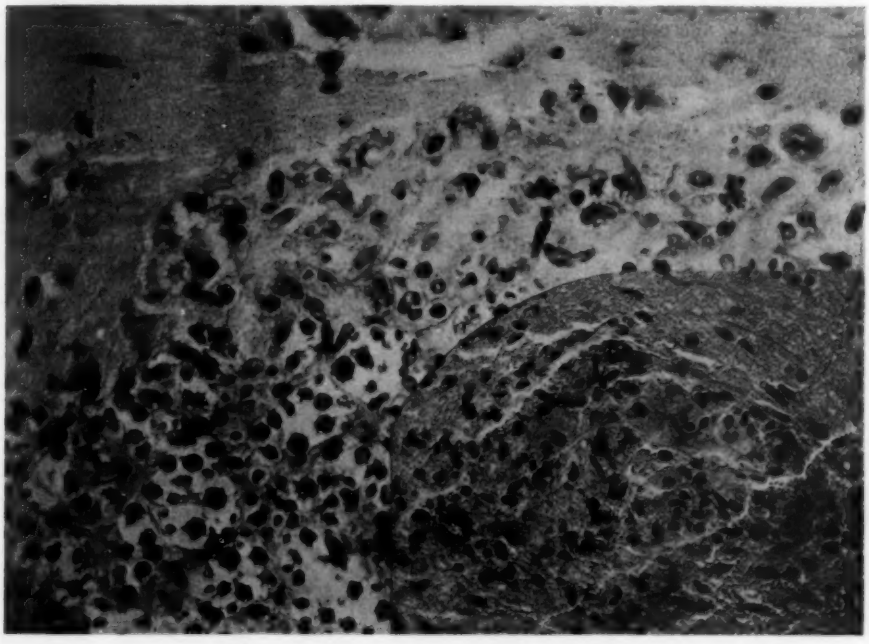


Fig. 4.—Wall of a cerebral cyst. The black spiculated bodies are yeast cells, which were distorted by the fixative. This field was selected to show endothelioid reaction rarely observed in the wall of a cyst. The insert shows a section of one of the granulomas rarely found in the spinal cord.

Summary of Histologic Observations.—A. Torular Phase: Yeast cells were most abundant in the meninges of the cerebrum, cerebellum and spinal cord, but cysts of the brain as well as the glomeruli and tubules of the kidneys also contained considerable numbers. They occurred sparingly in the pancreas and spleen. Whether the extensive chronic diffuse granulomatous changes in the latter might indicate that yeast cells were present at a previous time but had been destroyed or otherwise removed is a matter of speculation and will be discussed later in the paragraphs on Hodgkin's disease. They were not observed in the lungs or lymph nodes. Their absence in the latter is difficult to explain

in view of the fact that scrapings from lymph nodes had revealed them at necropsy and that they were present in tissue removed for biopsy.

As to the type of tissue reaction, it was consistent with that for Torula histolytica infection in general, i. e., either minimal or nil. In the brain substance and pancreas it was entirely absent. In the kidney it occurred in a mild, subacute form around some of the glomerular tufts and in the interstitial substance. In the cerebrospinal meninges there were a scattering of lymphoid cells and in places extensive hyperplasia of large, clear cells with rarefied cytoplasms, which were somewhat reminiscent of xanthoma cells. They were probably endothelial macrophages. In short, the severity and kind of tissue reaction varied from organ to organ.

B. Hodgkin's Disease: The major histologic problem of the case centered around the tissue reaction in the spleen and the lymph nodes, including the mediastinal mass.[3] In all sections there were (1) more or less loss of architecture and (2) reticulo-endothelial hyperplasia, with the presence of Dorothy Reed cells. The peribronchial lymph node exhibited such a degree of fibrosis that there could be no hesitation in diagnosing the changes as those of Hodgkin's disease; at least they were compatible with that disease. For the most part, however, the endothelial changes far overshadowed the lymphocytic and fibrous tissue changes, which for a long time delayed a final diagnosis of Hodgkin's disease. In principle, the reaction was an unusually massive, chronic diffuse, hyperplastic lymphadenitis, but peculiar in the same direction as obtains in Hodgkin's disease. Thus, it is admitted that such changes could still be produced by various agents, i. e., whether the process was torular in etiology or whether the conventional Hodgkin's disease was its basis, the end-result could be the same histologically. At this time we cannot decide finally which mechanism obtained in our patient, but it is at least permissible to submit a proposition in the same sense that the geometrician would open a problem for solution, namely, that T. histolytica is one of perhaps several micro-organisms which may evoke the histologic picture of Hodgkin's disease. The actual solution of the problem remains to be accomplished.

Comparing the histologic changes in the spleen, lymph nodes and mediastinal mass, successive steps can be traced between the obviously torular processes in the spleen and the processes definitely due to Hodgkin's disease in the lymph nodes and mediastinal mass. In the spleen, torula cells themselves (sometimes surrounded by granulomas) were seen; the grade of endothelial hyperplasia was mild, although there

3. Histologic sections were filed in the Army Medical Museum, Washington, D. C., (their number 36461) and in the Laboratory of Dermatological Research, University of Pennsylvania (accession number 2249).

was marked fibrosis. In the lymph nodes, in which the torula cells were absent, the endothelial cells were highly hyperplastic, and Dorothy Reed cells were observed. Fibrosis was present here also. In the mediastinal mass, endothelial features dominated; there were large numbers of Dorothy Reed cells, and, furthermore, the large size of the endothelial nuclei and the peripheral infiltrative characters indicated a high order of proliferative changes bordering on neoplasia. The interpretation placed on these observations is that the reticulo-endotheliosis was less active in the spleen, more highly developed in the lymph nodes and of severest grade—almost neoplastic—in the mediastinal mass. This is consistent with the gross anatomic findings.

Reconciliation of Torula Cells with Features of Hodgkin's Disease.—Such a reconciliation cannot be made readily in view of what has just been stated about (1) the presence of torula cells in a spleen that was far from the type seen in Hodgkin's disease histologically and (2) their absence, at least histologically, in the highly proliferative mediastinal mass which conformed more to the type seen in Hodgkin's disease. However, final decision should be reserved on this point when it is recalled that torular colonies were secured in cultures from the mediastinal mass. The possibility must be kept in mind that there are ultramicroscopic forms of Torula.

STUDIES OF CULTURES

The culture from our case was one of twenty strains of cerebrospinal Torulae which have been under systematic investigation in this laboratory over several years. Hence there was an unusually favorable opportunity for comparison with previously studied strains of cerebrospinal Torulae.

Solid Mediums.—On Pennsylvania medium [4] (a modified Sabouraud medium), colonies were not distinctive during the earlier stages of growth. They had a creamy, pasty quality which is common to monilias and several other species of yeast organisms. Growth was rapid, colonies attaining a diameter of 2 cm. within five weeks. At this time the colony was still pasty; it had a smooth, regular, moderately shiny surface, but had become creamy yellow. Within three months it had become deep cocoa brown, and the surface was nodular or lumpy. In some colonies the surface became divided (at about four weeks) into sectors, some of which became yet deeper brown with age and within which the surface was smooth instead of lumpy. This was an expression of dissociation—a feature which occurs in several other strains of cerebrospinal torulas. At times the colony became so soft as to flow to the bottom of the tube, which is highly characteristic for T. histolytica. However, Dr. Fitchett's strain was one of three in our series of twenty which tended to remain solid, as shown in figure 5 *A*. The fluid colony (fig. 5 *C*) was the more unusual. The medium underlying the colonies became turbid and brown. On bromphenol blue agar (p_H 4.6) the center of the colony was deep blue, while only the margins were brown.

4. Weidman, F. D., and Spring, Dorothy: Arch. Dermat. & Syph. **18**:829, 1928.

Fermentation Tests.—The material used as inoculum was tested for purity by both plating and direct examination of stained smears. Cultures from 4 to 5 days old, growing on Pennsylvania medium, served as the source of the inoculum. The test medium was the broth recommended by Castellani [5] in his extensive experiments on bronchial moniliasis. Bromcresol purple served as the indicator. The dulcite and arabinose broths were sterilized by passage through Berkefeld filters; the remaining fermentable substances were tristerilized in the Arnold apparatus. The material used in the control experiments consisted in a known highly active fermentor in the form of yeast, and in uninoculated tubes of the various solutions of sugar, which served as standard for comparison of

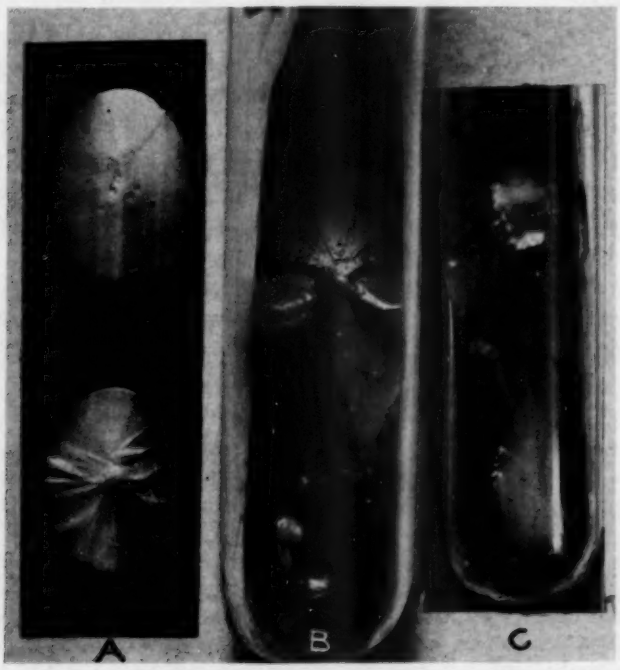


Fig. 5.—*A*, colony 1 month old (Pennsylvania medium); the elevated parts are expressions of dissociation. *B*, colony 2 months old; the darker (dissociated) sectors were pale chocolate brown. *C*, colony 10 weeks old; this is an example of the watery type of colony, with dripping to the bottom of the tube.

color. An additional control measure consisted in inoculations into tubes containing indicators but from which the sugar was omitted; this served as a test

5. Personal communication from Dr. Castellani. Meat extract is not to be employed on account of the small percentage of dextrose which it contains. However, 0.5 per cent sodium chloride is incorporated. Formula: To peptone water (peptone 1 per cent, sodium chloride 0.5 per cent) add 1 per cent of the desired sugar. This medium is approximately 1.5 per cent acid, and enough sodium hydroxide should be added to make it neutral (p_H 7). Castellani used litmus extract as an indicator for the production of acidity.

against fermentable constituents in the broth itself. The substances tested were: dextrose, maltose, dextrin, saccharose, galactose, mannite, lactose, salicin, dulcite, melitose, arabinose, adonitol, inulin, levulose and sorbite.

Within six days the production of acid by our strain was perceptible, and within nine days the acid reaction was strong, but only dextrose, levulose and saccharose were thus fermented. Readings were continued until the nineteenth day. Gas was not produced under our conditions (diffuse daylight at room temperature).

Compared with the entire series of twenty strains, our strain agreed in that not one culture produced gas. It agreed with three other strains as to the production of acid.[6] Incidentally, for the group as a whole it was found that there was considerable variation in the production of acid. At least dextrose and levulose were fermented by all twenty strains. To illustrate: Only dextrose and levulose were fermented by seven of the strains; dextrose, levulose and saccharose were fermented by four strains; melitose, dextrose, levulose and saccharose were fermented by four strains. Inulin, dextrose, levulose, saccharose and melitose were fermented by two strains, and these five sugars and mannite by two strains. T. histolytica is indeed a weak fermentor.

Microscopic Appearance in Culture.—In material from a 4 month old colony (the characteristics were more definite in old cultures), the features were those of a cryptococcus. Thus, hyphae were not produced, and asci were not demonstrable either after a sojourn of cells on plaster of paris blocks or by staining by Beauverie's technic.[7] The cells were fairly large and spherical or somewhat pyriform and had thick shells. Budding occurred only occasionally in these older cultures. Younger cells contained smaller or larger granules, while larger ones either had a solid hyaloid interior or contained coarse granules or spherules which stained red with sudan III. The latter were not sufficiently uniform in size or consistent in number (4 or multiples of 4) to indicate that they represented asci. The mucinoid envelop, which is characteristic of T. histolytica was readily demonstrated around many of the larger cells by the wet india ink technic (a solid particle of culture is stirred into a minute drop of india ink; the cover slip is applied immediately, and the particle is examined under the microscope). As compared with the other nineteen strains of the series studied, our strain had a particularly thick capsule in the sediment in fermentation tubes. The capsule was even thicker in the mediums containing inulin and adonitol. It was moderately thick in all the other sugars tested, except lactose and arabinose. In the latter two the capsule could not be identified.

Mycelium Formation.—While our strain was essentially nonmycelial, hyphae were occasionally observed in very old colonies (four months old). Such hyphae really represented highly elongated yeast cells, which, however, did not branch. They had a double contour. The interior contained small numbers of smaller and larger hyaloid spherules lying in a clear, colorless matrix. The terminus of such a cell frequently consisted of a series of coalescent knobby arrangements, each of which was reminiscent of one of the spherical cells but had not as yet

6. Analysis of the protocols of the cases represented by the three strains in respect to symptoms and morbid anatomy disclosed that the case of Freeman and Weidman fell into this fermentation group. The changes in that case resembling those in Hodgkin's disease will be discussed later.

7. Guillermond, A.: The Yeasts, translated by F. W. Tanner, New York, John Wiley & Sons, Inc., 1920, p. 52.

become abstricted from the elongated one. Freeman and Weidman[8] witnessed such formations on a previous occasion, but only in fluid medium which was very old, whereas with our strain it was also observed on solid medium. In any event, such pseudomycelium formation is to be regarded as exceptional and does not militate against classifying the organism as Torula.

In short, all the characteristics—gross, microscopic and biologic—were compatible with those which have already been postulated for T. histolytica, as understood at present. We have no hesitation in identifying the organism as such.

INOCULATION OF ANIMALS

Two cats, one white rat and one monkey were used. All the injections were made intrameningeally, except in the monkey, which was inoculated subcutaneously. A hole was made at the summit of the calvarium anteriorly with a small drill; the lesion was allowed to heal, and thereafter (from seven to ten days) injection was made by a hypodermic needle through the bony defect. In all cases an incision was made over the bone to secure a clear field, making certain that the material entered the meninges or at least the cranial cavity.

Cats.—Cat 1 received a freshly isolated culture from a rat which had been experimentally infected. Four and one-half weeks after injection it was killed, but examination gave negative results for infection with Torula. The second cat, which was inoculated with a culture which had not been (supposedly) increased in virulence by passage through a rat died within nine days. Small numbers of torula cells were observed in the washings of the meninges, but there were no recognizable torular lesions in the viscera. At most, the kidneys were large and white and had granular surfaces, suggesting chronic parenchymatous nephritis. There were a few small, turbid, gray markings in the liver suggesting focal necrosis. The solitary follicles in the spleen were enlarged.

Microscopically, the liver and kidneys were free from torular lesions. In the brain, however, there was marked thickening of the meninges as the result of round cell (largely plasma cell) infiltration. This extended well downward into the sulci, but there were no cysts present such as were seen in the human subject. There were torula cells in large numbers, some occurring in chains. The mucinoid envelop by which they were surrounded was not so heavy as is commonly observed. A further departure from the usual observations was the presence of numerous pink granules on the exterior of the yeast cell, such as are often seen on the conidia of aspergilli and certain other species of fungus. In short, the tissue reaction in this cat varied definitely from that seen in other experimental animals, first, in the scarcity of mucin around the yeast cells and, second, in the type of reactive cells. It appears that the infection managed to barely maintain a foothold and progressed but slowly, and that the parasite was growing in a vegetative rather than a parasitic way.

Rat.—The rat died sixteen days after inoculation. Lesions could not be identified at necropsy. Microscopically, the most severe involvement was observed in the meninges, which were thickened by the presence of torula cells. Lymphocytes were not numerous and were confined to certain accumulations around the larger blood vessels. Yeast cells occurred in such masses as to make deep indentations in the cerebral cortex, besides occurring as comparatively large cysts within

8. Freeman, W., and Weidman, F. D.: Arch. Neurol. & Psychiat. **9**:589, 1923.

its substance. There was no reaction around the cysts. In the pancreas there were several smaller or larger foci of torula cells. Some were large enough to be classified as small cysts. Most of them were not attended by a cellular reaction in the periphery; however, other foci were surrounded by a dense layer of lymphocytes. Giant cells and endothelioid cells were absent. The spleen, likewise, was affected, but only through the presence of three or four isolated individual cells, which were seen only after careful search through an entire histologic section. In the kidney there were a few clusters of torula cells in certain of the glomeruli. In neither of these organs was there any inflammatory reaction around the foci of yeast cells. Torula cells were not found in the liver. There was thus a definite parallelism between the infection in man and in the rat, as to both the

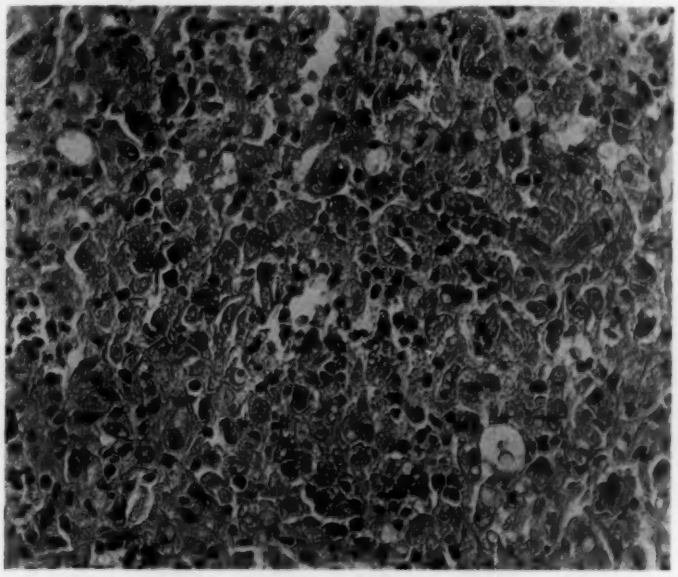


Fig. 6.—Nodule in scalp of an experimental cat; the circular space contains a budding torula cell.

organ involved and the extent of the involvement. The changes resembling those in Hodgkin's disease, however, were not reproduced.

Monkey.—A Macacus rhesus was inoculated intradermally in the shoulder and the groin. The tests were confined to the skin in this animal, because they were incidental to studies of cutaneous torulosis in man, in which it was sought to learn whether the skin could serve as a portal of entry and whether intradermal injection would be followed by generalized infection. Our strain was the one selected for inoculation. Within a week a nodule 2 cm. in diameter had developed, which was soft like an abscess but which did not exhibit any surrounding congestion. The summit of the nodule sloughed, revealing an underlying core; small quantities of pus exuded, which contained enormous numbers of torula cells. The entire lesion regressed spontaneously within two weeks, leaving a dense scar. The animal died of enteritis two months after inoculation, but did not exhibit any torular lesions of the viscera or brain at necropsy. In short, whereas frank lesions developed in

the skin, metastasis did not take place to the internal organs. The details of these experiments will be found recorded by one of us [9] in another place.

Endotheliosis in Experimental Animals Resembling That in Hodgkin's Disease.—In connection with this series of twenty strains of Torula previously cited, intrameningeal inoculations were made over a period of several years into cats, white rats and mice. The spleen and lymph nodes of all these animals so far as these were available, were restudied by us with special reference to changes resembling those in Hodgkin's disease. Unfortunately, the lymph nodes had been preserved for microscopic examination in only a few cases, because only the torula cell entered into consideration at that time. There thus remained for the present study the following materials: thirteen spleens and three lymph nodes of rats and four spleens and three lymph nodes of cats.

In only one animal, a cat, was anything observed which approached the changes resembling those of Hodgkin's disease in our patient. Thus, immediately anterior to the primary site of inoculation on the scalp was a nodule 2 mm. in diameter. Histologically, it consisted of indefinitely outlined, more or less stellate cells richly disposed on a delicate reticulum; i. e., the histologic picture was precisely that seen in the mediastinal mass of our patient, with the presence, in addition, of rather numerous torula cells. In the rats there was a definite tendency toward fibrillar fibrosis in the reticulum of the spleen, together with increase of the macrocytes, which are normal in the spleen of that animal. There was also definite hyperplasia of certain large splenocytes, which occurred in small numbers around the splenic nodules of the rats. In general, however, there were no definite changes of Hodgkin's disease in any of the animals, except in the cat first mentioned. The changes in this animal, however, were such as cannot be reconciled with those of any previously described torulosis. At the same time, they were so distinctive and reproduced so faithfully the histologic picture in the mediastinal mass of our human subject that they must have some relation to the torular processes. It should be recalled, however, that none of the rats lived longer than seven weeks after inoculation—entirely too brief a period within which definite changes of Hodgkin's disease should be expected to occur.

COMMENT

In Freeman's [1] extensive monograph only three instances of multiple visceral involvement are described. In our patient the kidneys were severely involved, and the pancreas, spleen and lymph nodes were definitely affected, to say nothing of the cerebrospinal involvement. Only the lungs (the liver was not available for histologic examination) were unaffected. Incidentally, the renal involvement brings attention to the urine as an additional source of identification of torulosis; according to Freeman's monograph, the yeast cell was found in urine once—in his case 5. This was also a case with extremely wide involvement of the viscera, particularly of the lymph nodes. There can be little doubt that there was invasion of the blood stream in our patient; this was proved by the presence of torula cells in renal blood vessels; yet the blood culture was negative.

---

9. Weidman, F. D.: South. M. J. **26**:851, 1933.

Relationship to Hodgkin's Disease.—Hodgkin's disease, to say nothing of tuberculosis, has already been touched on in the literature of torular infection. It would seem to be more than a coincidence that a condition like Hodgkin's disease, which is excessively rare like torulosis, is the one to receive mention, to say nothing of the suggestive relation which we observed in our patient. Indeed, it is cited specifically in the report of two of the forty-four instances collected by Freeman (that of Freeman and Weidman and that of Smith and Crawford). Thus,

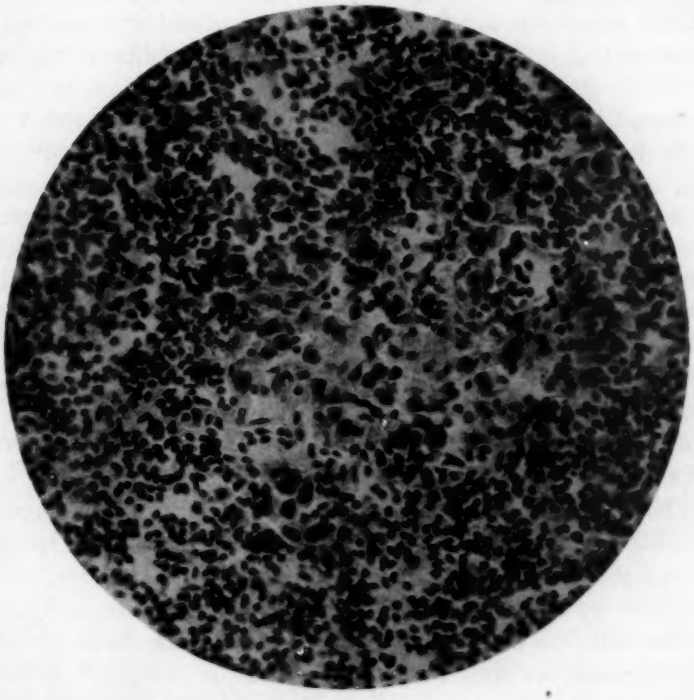


Fig. 7.—Section of mesenteric lymph nodes in Freeman and Weidman's case, showing a localized focus with Dorothy Reed cells.

in Freeman and Weidman's case there were enlarged nodes in the left axilla and about the head of the pancreas, the largest measuring 9 by 5 by 2.5 cm. Furthermore, biopsy performed five years previously had shown Hodgkin's disease, and the nodes had diminished under irradiation therapy. However, the nodes examined at necropsy were not quite typical of Hodgkin's disease, although they were highly suggestive, and the determination of a specific infectious factor (Torula) assisted in dismissing serious considerations of Hodgkin's disease. No yeast organisms were found in sections of lymph nodes secured at necropsy, but when used for the inoculation of guinea-pigs they were recovered

from the nodes at the head of the pancreas. It should be recorded, at least, that the strain from this subject fermented dextrose, levulose and saccharose, i. e., the same group that was fermented by our own strain. Since two other strains among the twenty which we studied also fell into this group, special significance cannot be invoked, at least not at present.

Although there was no enlargement of lymph nodes in Smith and Crawford's case, there was swelling over the left scapula, which was regarded histologically as atypical of Hodgkin's disease. This lesion was examined seventeen months before necropsy. After necropsy, when the diagnosis of torulosis had been made, reexamination of the sections disclosed the presence of Torula.

Enlargement of lymph nodes due to a nontorular agent, i. e., the tubercle bacillus, has occurred frequently in torulosis, without provoking thoughts particularly of Hodgkin's disease. In one such case there was cervical adenopathy (Türk), and in a second the lymph nodes were removed surgically a number of years previously (in Evans' second case). Enlargement of mediastinal nodes and "acute inflamed" mesenteric nodes were found in Williams'[10] patient, but were not examined microscopically. Furthermore, in the patient studied by Rusk and Farnell there was an abscess of the axilla which was very slow in healing. A chronic axillary abscess also occurred in Wildman's case and in Rusk and Farnell's second case. Further details of the foregoing cases will be found in Freeman's monograph.

In both the cases just cited it may be noticed that the diagnosis of Hodgkin's disease was made with decided reservations. We reexamined the original sections in the case of Freeman and Weidman, searching particularly for torula cells which might have been overlooked, but must leave the situation as originally stated; that is, the histologic changes were suggestive, but were not definitely those of Hodgkin's disease. As there were not sufficient clinical symptoms, such as anemia and pronounced adenopathy, to support the histopathologic changes, we feel constrained to exclude all these cases as Hodgkin's disease and to surmise that they were but instances of general, low grade lymphadenitis such as are often classified simply as adenopathies.

But at such a juncture consideration of our own case enters to give a special and renewed significance, because the symptoms were so definitely those of Hodgkin's disease that there was no hesitation in making that diagnosis clinically. Thus, the emaciation bespoke extreme weakness, and there were definite anemia and marked adenopathy. The question at issue is whether the torulosis was responsible for the symp-

10. Williams, J. R.: M. J. Australia **2**:185, 1922.

toms of Hodgkin's disease, i. e., whether it is one of several organisms or noxae which may induce such symptoms, or whether the torulosis was superimposed on preceding Hodgkin's disease. The occurrence of torula cells in the lymph nodes, in both the specimen secured at biopsy and the specimens obtained at necropsy throws additional suspicion on torulosis as the etiologic agent, but without quite incriminating it. (It may be recalled that Torula was also cultured from lymph nodes at the head of the pancreas in Weidman and Freeman's case.) It can be explained just as reasonably that with such extensive systemic involvement there was obviously an infection of the blood stream, and that lymph nodes should be expected to participate equally with the kidney, pancreas and other organs.

One cannot dismiss the association of these two diseases summarily, in view of both the unsettled status of the causation of Hodgkin's disease (also its scope and limitations, such as Hodgkin's sarcoma) and the possibility that peculiarities in the constitution of persons or of their lymph glands might permit the development of symptoms of Hodgkin's disease from a torular lesion as well as from infection due to the tubercle bacillus, the pseudodiphtheria bacillus and other microorganisms which have from time to time been advanced as etiologic agents in Hodgkin's disease. In any event, the torular reaction might well serve as a tool in the investigation of the etiology of Hodgkin's disease as revealed histologically. Similarly, since the cells do not always show up well in routine hematoxylin and eosin sections, special precautions should be taken to attempt to demonstrate them in the brain in future cases of Hodgkin's disease, at least if there are neurologic symptoms.

Type of Tissue Reaction Against Torula Cells.—This conformed with that of other cases of infection with T. histolytica; i. e., it was either absent or scanty in the brain substance and generally scanty but sometimes tuberculoid in the other organs.

Portal of Entry.—This topic merits special attention here only in case it is concluded that the yeast cells were the cause of the generalized lymphadenopathy. In that case the intestines would appear to have been the primary portal of entry instead of the lungs and the nasopharyngeal passages, as is usually the case in torulosis. Such a portal is entirely consistent with the biology of yeast cells; this is illustrated by the fact that Tanaka [11] observed 10 per cent Saccharomyces in apparently normal mesenteric lymph nodes examined at necropsy.

Pathogenicity of the Micro-Organism.—This particular strain conformed to others of T. histolytica in being pathogenic for the white rat but not for the cat. It was also pathogenic for the skin of a monkey.

11. Tanaka: J. Path. & Bact. **23**:350, 1920.

SUMMARY

The fourth case of widespread, generalized torulosis, which is usually confined to the cerebrospinal nervous system, is reported. It occurred in a Negro, 18 years of age, who had had symptoms of Hodgkin's disease for three years. In forty-four collected instances there have been two additional cases in which the histologic picture of Hodgkin's disease was also approached, but only in our own case has the full symptomatology (weakness, anemia and massive adenopathy) of Hodgkin's disease been recorded. Nevertheless, it would be premature to regard torular infection as one of the causative agents of Hodgkin's disease, although changes were highly suggestive of such an etiology. The presence of extensive renal involvement calls attention to the necessity for examination of the urine for torula cells as they have been observed in the urine at least once. Attention is called anew to the possibility that the intestines may serve as the primary portal of entry for torulosis. Cases of Hodgkin's disease with meningeal symptoms demand examination for torular infection.

INFLUENCE OF VARIOUS DIETS ON EXPERIMENTAL AMYLOIDOSIS IN MICE

D. Y. KU, M.D.†
WOOSUNG, CHINA
AND
M. A. SIMON, M.D.
CLEVELAND

Amyloidosis is found only infrequently at autopsy in China, although chronic tuberculosis, osteomyelitis and other kinds of chronic suppurative processes are more common than in the western countries. Kuczynski [1] reported the infrequency of amyloidosis also in the Japanese. Tanaka [2] stated that no advanced cases of amyloidosis have been observed in Japan but that in cases of chronic suppuration the occurrence of microscopic deposits of amyloid is frequent. He attributed the milder degree of amyloidosis to the low protein content of the diet of the Chinese and Japanese. Kuczynski [1] produced amyloidosis in mice not only by parenteral injection of nutrose but also by feeding them certain proteins such as nutrose and cheese. He believes that a protein diet favors the production of amyloid. This has been disputed by Jaffé.[3] According to him the amyloidosis which develops in mice fed on cheese, as in Kuczynski's experiments, is caused by the enteritis which may develop and is not due directly to the cheese. From Jaffé's experiments, it appears that the protein diet as well as cholesterol and fat can delay the development of experimental amyloidosis in mice. According to Grayzel [4] and his collaborators, mice fed on liver preparations are not susceptible to amyloid degeneration. These discrepancies and the fact that in autopsy material in China and Japan severe amyloidosis appears to be uncommon led us to undertake the following experiments.

MATERIAL AND METHODS

Series A.—White male mice were used. The exact age was not known, but all weighed between 25 and 30 Gm. at the beginning of the experiment. The animals were divided into four groups. One group was fed on a diet containing a large

† Fellow in Medicine, Rockefeller Foundation, from National Central University.
Aided by a grant from the Rockefeller Foundation.
From the Institute of Pathology, Western Reserve University and University Hospitals.

1. Kuczynski, M. H.: Klin. Wchnschr. **2**:727, 1923.
2. Tanaka, Y.: München. med. Wchnschr. **57**:1383, 1910.
3. Jaffé, R. H.: Arch. Path. **2**:149, 1926.
4. Grayzel, H. G.; Jacobi, M.; Maslow, H., and Warshall, H. B.: Proc. Soc. Exper. Biol. & Med. **28**:172, 1930.

amount of animal protein and just enough other substances to sustain life. The composition of the diet was as follows: meat scrap powder,[5] 91 parts; brewer's yeast, 5 parts; cod liver oil, 2 parts, and agar-agar, 2 parts.

The second group of mice was fed on a diet containing a large amount of plant proteins and the necessary quantity of adjuvant substances to make the diet adequate to sustain life. It was composed of 91 parts of soy bean flour,[6] 4 parts of brewer's yeast, 1 part of cod liver oil and 4 parts of the following mixture:

	Gm. or Cc.
Sodium chloride (NaCl)	0.173
Magnesium sulphate (anhydrous) ($MgSO_4$)	0.266
Monosodium phosphate ($NaH_2PO_4.H_2O$)	0.347
Dipotassium phosphate (K_2HPO_4)	0.954
Monocalcium phosphate ($CaH_4(PO_4)_2.H_2O$)	0.540
Ferrous citrate	0.118
Calcium lactate	1.300

The third group of mice were given a diet consisting chiefly of carbohydrate. Its composition was as follows corn-starch, 73 parts; soy bean flour, 15 parts; cod liver oil, 2 parts; brewer's yeast, 5 parts, and the aforementioned mixture, 5 parts.

The fourth group was fed on a normal stock diet consisting of: ground corn, 600 Gm.; cracked wheat, 300 Gm.; dried milk, 60 Gm.; meat scrap, 90 Gm.; sodium chloride, 10 Gm., and lettuce, hard bread and milk.

Water was given *ad libitum* to the four groups. The mice were fed on these diets for at least thirty-five days preceding the first injection in order to adapt them to the new diets. Then they were given daily 0.5 cc. of 3 per cent sterile solution of nutrose in physiologic solution of sodium chloride by intramuscular injection into both hindlegs. All the mice, other than those which died spontaneously or were killed when in moribund condition during the early period of the experiment, were killed by inhalation of chloroform after receiving thirty daily injections. Cultures were taken from the muscles of the hindlegs of all the mice which died before the completion of the series and also from the majority of those which were killed. Since the spleen, liver and kidneys are considered by all authors as the most common and constant sites of amyloid deposition, portions of these three organs were fixed in 10 per cent solution of formaldehyde and in 80 per cent alcohol. Paraffin sections were stained with hematoxylin and eosin and with congo red.

Series B.—Another group of similar experiments was carried out with the following differences in technic: Fifty daily injections were given instead of thirty. Animals which did not receive injections were fed the diets for eighty days to see whether spontaneous amyloidosis developed. A small number of animals was fed on the stock diets for thirty days and then given fifty daily intramuscular injections of sterile saline solution. In this series of animals the sites of injection were not examined bacteriologically for possible infection, but all the animals found to be suffering from gross infection were discarded.

---

5. The meat scrap powder contains 50 per cent protein. No salt mixture was added to this material because of the high inorganic salt content found on analysis, which showed: total chlorides (calculated as sodium chloride), 0.96 per cent; calcium (high ground bone content), 11.0 per cent, and phosphorus, 4.3 per cent. These figures give the percentage by weight.

6. The percentage of protein in soy bean flour is from 41 to 43 per cent.

Sections of liver, spleen and kidney from the latter experimental animals were fixed in 80 per cent alcohol and in Zenker's fluid to which a dilute solution of formaldehyde had been added. Methyl violet and Mallory's aniline blue stains were employed.

The results are best illustrated by the accompanying tables.

TABLE 1.—*Series A, Animals Which Received Injections of Nutrose*

Diet	Number of Daily Injections	Number of Animals Receiving Injections	Number of Animals Showing Deposits of Amyloid
Meat scrap	30	14	6
Soy bean	30	12	5
Carbohydrate	30	16	2

TABLE 2.—*Series B, Animals Which Received Injections of Nutrose*

Diet	Number of Daily Injections	Number of Animals Receiving Injections	Number of Animals Showing Deposits of Amyloid
Normal	50	16	9
Meat scrap	50	13	6
Soy bean	50	26	7
Carbohydrate	50	18	0

TABLE 3.—*Animals Receiving Injections of Saline Solution*

Diet	Number of Daily Injections	Number of Animals Receiving Injections	Number of Animals Showing Deposits of Amyloid
Normal	50	6	2
Meat scrap	50	8	0
Soy bean	50	5	1
Carbohydrate	50	6	2

TABLE 4.—*Animals Which Did Not Receive Injections*

Diet	Number of Animals in Group	Number of Animals Showing Deposits of Amyloid
Normal	10	0
Meat scrap	11	0
Soy bean	12	0
Carbohydrate	11	0

TABLE 5.—*Combined Results of Series A and B, Animals Receiving Injections of Nutrose*

Diet	Total Animals in Experiment	Number Showing Deposits of Amyloid	Number Not Showing Deposits of Amyloid	Percentage Positive
Meat scrap	27	12	15	44.4
Soy bean	38	12	26	32.1
High carbohydrate	34	2	32	5.8
Normal	16	9	7	56.0

The spleen was found to be the most constant site of amyloid; this is well known and agreed on by all authors. In animals in which the specific staining of amyloid was at first doubtful, restains were performed (with controls) on the spleen with methyl violet and, when positive, the results were interpreted as positive in the other tissues and vice versa.

Histologically the pictures were similar to those described and illustrated by Jaffé.[7] In addition, a considerable number of giant cells which showed rose-colored amorphous material when stained with methyl violet were seen in the spleen. This picture corresponds to the "precursor" stage of amyloid as described by Grayzel.[8] Such evidence of amyloidosis alone was not considered positive for our diagnosis, and only in cases in which the amounts were unequivocal was a positive diagnosis for amyloid made.

COMMENT

The greatest percentage of mice showing amyloidosis occurred in the group fed on normal diets, while the group fed on a high carbohydrate diet showed the smallest percentage. The severity of the change was not appreciably greater in any specific group.

The percentage of mice showing amyloidosis was strikingly low in the group fed on the high carbohydrate diet. The difference is one of frequency of occurrence rather than of degree of change in the individual mice of the different groups. It is evident that mice on normal, meat and soy bean diets, all containing protein, were susceptible to amyloidosis. The results do not contradict Kuczynski's[9] assumption that a protein diet favors the experimental production of amyloidosis in mice.

Kuczynski,[9] using cheese and egg albumin, and Smetana,[10] using Swiss cheese, found that the high protein diet favored the production of amyloidosis in mice, while Jaffé[3] found that beef heart powder not only delayed the formation of amyloid but even "protected" mice against it. According to Grayzel[4] and his collaborators, liver powder had an effect similar to that of beef heart powder and delayed the production of amyloid in mice. Grayzel[8] also stated that resorption is accelerated by liver once the injections are discontinued, provided advanced amyloidosis has not set in. It appears that not all proteins have the same effect in influencing the production of amyloid in mice. Furthermore, the standard laboratory diet—consisting of white bread,

7. Jaffé, R. H.: Arch. Path. **1**:25, 1926.

8. Grayzel, H. G.; Jacobi, M.; Warshall, H. B.; Bogin, M., and Bolker, H.: Arch. Path. **17**:50, 1934.

9. Kuczynski, M. H.: Virchows Arch. f. path. Anat. **239**:185, 1922.

10. Smetana, H.: Bull. Johns Hopkins Hosp. **37**:383, 1925.

oats and skimmed milk—in Jaffé's experiments—as well as Grayzel's [8] standard diet favored amyloidosis in mice, whereas we observed that the mice fed chiefly on corn-starch were not likely to show the change. Whether corn-starch exerts a protecting effect on experimental amyloidosis in mice as produced by injections of nutrose or whether the effect is due to the failure to ingest sufficient amounts of the substances which may be necessary for the formation or deposition of amyloid is not determined. Therefore, the influence of different kinds of carbohydrate may also differ. It is probable that the kind of protein or of carbohydrate favors the formation of, or protects against, amyloid, respectively. Even if Kuczynski's theory that a diet high in protein favors experimental amyloidosis were accepted fully, our results could hardly be applied to human pathology. Although the Chinese eat soy bean in many forms and in considerable quantity, cases of amyloidosis are seldom observed in China.

Although many investigators have used Kuczynski's [1] method of producing amyloidosis in mice, no critical application to human pathology is found in the literature. Nutrose is definitely accepted by all authors as a substance efficient in inducing experimental amyloidosis, yet there is no absolute certainty in that respect. According to Letterer [11] it is not possible to produce amyloid in every case by parenteral administration of nutrose, but Smetana [10] claimed almost 100 per cent positive results after thirty injections of solution of nutrose. It appears that the type of stock diet used modifies to a great extent the time and number of injections required to produce experimental amyloidosis by parenteral injections. This factor is well shown in Grayzel's [8] work. In his group of mice in which various combinations of vitamins were used the total incidence of amyloid, even after as many as sixty-seven injections, was strikingly low. Uchino [12] emphasized the added effect of bacterial infection which, according to our study, is a sufficient but not a necessary condition for the development of amyloid and may act as an adjuvant. In a number of the control animals, even in the group fed on a carbohydrate diet and receiving injections of sterile saline solution, positive amyloid reaction occurred. This may indicate that corn-starch, while it appears to exert a protecting influence on experimental amyloidosis as produced by nutrose, is not so efficient when infection is present. Although no bacteriologic examinations were made, it is assumed that the probable explanation for amyloidosis in these animals must have been infection, for no amyloidosis developed in any of the animals which did not receive injections, regardless of what diet they were fed.

---

11. Letterer, E.: Verhandl. d. deutsch. path. Gesellsch. **20**:301, 1925.
12. Uchino, S.: Beitr. z. path. Anat. u. z. allg. Path. **74**:405, 1925.

The exact nature of human amyloid remains obscure. In a summary review of Leupold [13] the differences of opinion of various investigators about this question is well discussed. No attempt at chemical analysis of the experimental amyloid appears to have been made. The supposed identity of experimental and of human amyloid has been based on the morphologic appearance. Staining reactions vary. The iodine and methyl violet stains are not always positive; this has also been observed by Smetana. Our results showed a fairly good accord between methyl violet and Mallory's aniline blue. Fairly good results were obtained with congo red.

All authors agree only on the statement that animal and human amyloid belong to the same type of protein compound. Karczag, Paunz and Németh [14] expressed the opinion that animal amyloid is a prephase of the human type. The mode of formation of amyloid in animals and human beings appears to be different. In animals we always observed a perifollicular deposition of amyloid in the spleen but rarely in the form of the sago spleen. Strasser [15] expressed a belief that in the liver of mice the formation of amyloid does not begin in the intermediate zone but usually starts in the wall of blood vessels in the interlobular spaces. The "precursor" stage described by Grayzel [8] cannot be evaluated at this time.

Owing to the lack of knowledge of the chemical nature of amyloid and to the inconstancy of characteristic staining properties of animal amyloid it is impossible to apply our results directly to human disease.

SUMMARY AND CONCLUSIONS

The influence of different kinds of diet on experimental amyloidosis produced in mice by the intramuscular injection of a solution of nutrose was investigated. Four kinds of diets were used. Three consisted mainly of meat scrap, soy bean and corn-starch, respectively (with the necessary supplement of minerals and vitamins). The fourth was the stock mixed diet for mice.

The mice fed on the normal diet showed the largest percentage of amyloidosis; the group fed on high protein diet came next, and the smallest percentage was found in the group fed on a diet rich in corn-starch. Control animals receiving injections of saline solution instead of nutrose also showed amyloid. Untreated control animals showed no amyloid.

---

13. Leupold, E.: Ergebn. d. allg. Path. u path. Anat. **21**:120, 1925-26; Beitr. z. path. Anat. u. z. allg. Path. **64**:347, 1918.

14. Karczag, L.; Paunz, L., and Németh, L.: Ztschr. f. d. ges. exper. Med. **41**:71, 1924.

15. Strasser, U.: Ztschr. f. d. ges. exper. Med. **36**:388, 1923.

A diet high in carbohydrate delays, protects against or fails to provide the necessary building material for the deposition of experimental amyloidosis produced in mice by injections of nutrose.

The difference between the changes in the three groups consisted more in the percentage than in the degree of severity of the changes in the individual mice.

The fact that a large percentage of mice showed positive results when fed on relatively high protein diets (both animal and plant proteins) agrees with Kuczynski's assumption that a protein diet favors the production of amyloidosis but contradicts the results of Jaffé's experiments.

Soy bean is a popular food in China. Amyloidosis is rarely found at autopsy in Chinese. The condition developed in a high percentage of mice fed on a soy bean diet and given injections of nutrose. Therefore, the low incidence of amyloidosis cannot be attributed to this feature of the Chinese diet. Even animals fed on the same diet and receiving daily injections of the same amount of nutrose exhibit individual variations of susceptibility to experimental amyloidosis. Similar variations probably exist in human amyloidosis. The inadequacy of our methods for the specific demonstration of amyloid may also play a part in the results obtained.

A CHEMICAL STUDY OF ARTERIOSCLEROTIC LESIONS IN THE HUMAN AORTA

DOROTHY R. MEEKER, A.B.
AND
JAMES W. JOBLING, M.D.
NEW YORK

In spite of the large amount of experimental work that has been done on arteriosclerosis there are surprisingly few chemical studies of the human arteriosclerotic aorta. Gazert,[1] in 1899, published the first series of fat, calcium and nitrogen determinations on arteriosclerotic aortas. He showed that there was an increase of fat, ash and calcium, and a decrease of nitrogen, as the arteriosclerotic changes became more extensive. In 1906, Baldauf [2] again demonstrated the increase of fat, and at the same time a decrease of phosphatids with increasing calcification. Then, after Aschoff had demonstrated that a large part of the fatty material in arteriosclerotic plaques was cholesterol ester, Windaus,[3] in 1910, analyzed normal and atheromatous aortas for cholesterol and cholesterol esters and showed that atheromatous aortas have from six to seven times as much free, and twenty to twenty-six times as much bound, cholesterol as normal aortas. The next important work was done in 1926 by Schönheimer [4] who, with more modern methods, again demonstrated the increase of cholesterol and cholesterol esters. All this previous work, however, was done on extracts of whole aortas; therefore it seemed to us worth while to try to isolate, for analysis, the portions involved in intimal lesions apart from the other portions of the aorta. In this way, it was hoped to obtain a more accurate picture of the changes in the pathologic tissue alone.

ANALYSES

The material used consisted of fresh, unfixed human aortas taken at autopsy from patients showing the usual variety of diseases found in a metropolitan hospital. The intima and part of the media were stripped away from the adventitia,

This investigation has been aided by a grant from the Josiah Macy Jr. Foundation.

From the Department of Pathology, College of Physicians and Surgeons, Columbia University.

1. Gazert: Deutsches Arch. f. klin. Med. **62**:390, 1899.
2. Baldauf, L. K.: J. M. Research **15**:355, 1906.
3. Windaus, A.: Ztschr. f. physiol. Chem. **67**:174, 1910.
4. Schönheimer, R.: Ztschr. f. physiol. Chem. **160**:61, 1926; **177**:143, 1928.

laid with the intima down, and the media stripped off as completely as possible with a forceps and knife. The intima was then turned over, and the atherosclerotic plaques were cut out of it and classified as early, medium or late. As a control, normal intimal tissue was cut out in the same way. The early lesions were small, slightly raised, yellowish, opaque, glistening plaques, which are usually found in the arch, and may also form a streak down the posterior wall of the aorta about the orifices of the intercostal arteries. The medium lesions were thicker, yellow and gray, partly translucent plaques, containing hyalinized connective tissue and often grossly visible fat deposits. The late lesions were extensively hyalinized, calcified or ulcerated tissue.

The plaques were weighed, transferred to a paper thimble (which had been previously extracted with boiling alcohol) hung in a flask fitted with a reflux condenser and extracted continuously with boiling 95 per cent alcohol for from three to four hours. The contents of the flask were then cooled and filtered through a fat-free filter paper into a volumetric flask of appropriate size. The thimble and flask were further extracted and washed several times with ether, and the ether extracts added to the alcohol extract through the same filter, and the filter was finally washed with a little more ether. The combined extracts were then made up to volume with ether. This alcohol-ether extract was used for all the analyses. (The completeness of this extraction was checked several times by repeating the foregoing process. The weight of the residue was never more than from 1 to 2 per cent of that of the original extract.)

For the determination of the dry weight of the fatty extract, part of the original extract was dried down in a beaker, reextracted with ether, dried again, reextracted with boiling petroleum ether (boiling point from 40 to 60 C.), filtered, dried first on the steam bath and finally in a vacuum desiccator over night, and then weighed. In some cases in which the amount of fat was small, this weighed sample was redissolved in chloroform, made up to its original volume and used for the determinations of phosphorus.

Determination of Phosphorus.—The foregoing extract was dried down in a large pyrex test tube and ashed with perchloric and nitric acids until the solution was colorless. The process is necessarily very slow, since overheating may drive off some phosphorus. It was then transferred quantitatively to a 25 cc. volumetric flask, neutralized to phenolphthalein with concentrated sodium hydroxide, and the phosphorus determined by the method of Fiske and Subbarrow.[5] Duplicates ordinarily checked within 5 per cent. From the phosphorus values, phospholipids were calculated as lecithin (molecular weight 810).

The cholesterol and cholesterol ester were determined on the original alcohol-ether extracts by a method devised by Schönheimer and Sperry, which will be published shortly.[6] Duplicates always checked within 5 per cent and ordinarily within 2 per cent. The determinations actually gave values for total and for free cholesterol. The ester fraction was obtained by difference and calculated as cholesterol oleate (in the ninth column of the accompanying table).

The cases have been arranged in groups according to the classification of the tissue as normal or as showing early, medium or late lesions, and within the separate groups the cases have been arranged according to increasing age.

---

5. Fiske, C. H., and Subbarrow, Y.: J. Biol. Chem. **66**:375, 1925.

6. Dr. Warren Sperry of the Babies Hospital made the cholesterol determinations.

Tissue Used for Analysis	Age, Years	Wet Weight of Tissue, Gm.	Fatty Extract, per Cent of Wet Weight of Tissue	Phospholipids, per Cent of Fatty Extract	Total Cholesterol, per Cent of Fatty Extract	Ester Cholesterol, per Cent of Total Fatty Extract	Free Cholesterol, per Cent of Total Fatty Extract
Normal tissue	12	1.46	0.87	26.1	16.2	3.01	13.2
	27	2.18	0.95	26.9	27.4	13.9	13.5
	29	2.23	1.48	26.5	27.8	13.3	14.5
	31	1.27	1.83	21.4	27.2	15.1	12.1
	60	1.88	0.90	16.3	31.2	19.4	11.8
	60	1.94	2.22	17.9	33.7	24.4	9.3
Early lesions	21-26	2.29	3.23	16.2	40.5	28.4	12.1
	27-28	2.49	3.84	19.7	41.6	31.2	10.4
	26-30	1.51	3.90	14.2	39.0	27.2	11.9
	32	1.55	4.32	21.6	40.2	22.4	17.9
	37	1.45	2.76	18.7	37.5	25.0	12.5
	37-39	2.11	6.10	15.5	48.4	32.6	15.9
	38	1.83	4.90	18.9	38.9	18.9	20.0
	42	2.06	4.55	17.5	43.6	27.7	16.0
	43†	1.58	5.32	13.1	45.2	36.9	8.3
	45	3.31	11.90	18.9	43.7	22.5	21.2
	50	2.06	3.89	16.3	42.5	31.2	11.2
	52-60	2.24	5.85	16.8	48.8	30.6	18.3
Average			5.04	17.3	42.5	27.9	14.7
Medium lesions	21	1.23	3.34	12.2	44.4	32.4	12.2
	50	2.02	4.55	16.3	40.2	26.1	14.1
	52	2.45	6.20	12.2	46.6	28.3	18.4
	52†	3.75	8.98	21.6	49.5	29.7	19.8
	52	1.39	6.25	14.9	52.8	24.1	28.7
	53	2.41	8.95	18.6	50.2	26.5	23.7
	56†	2.01	9.50	18.0	54.0	37.5	16.5
	57	5.33	7.82	19.9	43.3	26.9	16.3
	57†	3.47	8.97	15.5	49.3	31.8	17.3
	57	1.75	4.97	19.1	43.6	24.2	19.0
	60	1.10	8.63	....	49.5	24.2	25.3
	66†	1.63	9.61	21.0	50.9	24.8	26.1
Average			7.19	17.2	47.7	28.3	19.2
Late lesions	43†	2.59	6.55	12.4	49.4	27.0	22.4
	46-53	3.06	9.83	13.0	53.2	30.5	22.6
	49	1.18	10.85	....	46.1	22.7	23.4
	52†	4.48	8.57	13.8	52.1	31.3	20.8
	55	2.00	6.70	17.9	51.5	26.1	25.4
	56†	4.89	7.55	17.1	50.4	21.9	28.5
	57†	5.06	7.87	18.0	51.4	31.4	19.8
	59	5.77	10.90	18.3	49.6	23.1	26.5
	60	4.62	4.19	18.7	51.1	26.9	24.3
	62	2.37	8.05	16.3	52.3	19.9	32.4
	62	9.79	7.55	16.4	48.1	31.1	16.9
	66†	3.13	14.50	20.0	56.6	20.9	35.7
	66	10.78	7.96	17.9	52.8	23.5	29.2
	73	6.85	5.39	17.4	45.8	22.8	23.0
	74	12.03	9.29	19.2	54.6	24.2	30.4
Average			8.38	16.9	51.0	25.5	25.4

* In the table the averages have been calculated to show conveniently the tendencies which we have discussed. The variations in the groups are too large to give the averages exact mathematical significance.

† Cases in which both early and late or both medium and late lesions were taken from the aorta.

*Forty-Five Human Aortas to Determine Phospholipid and Cholesterol Values**

Free Cholesterol Plus Bound Cholesterol (as Oleate), per Cent of Total Fatty Extract	Free Cholesterol-Ester Cholesterol Quotient	Diagnosis
18.5	4.00	Rheumatic heart
38.0	0.97	Rheumatic endocarditis
38.0	1.09	Generalized peritonitis (perforated ulcer)
38.8	0.80	Glomerular nephritis (hypertension)
45.9	0.61	Carcinoma of rectum (advanced arteriosclerosis)
52.3	0.38	Medial calcification of aorta
62.2	0.43	Four cases—rheumatic endocarditis; bacterial endocarditis; brain abscess and meningitis; meningitis
65.6	0.33	Adenocarcinoma of rectum, papillary cystadenoma of ovary
59.3	0.44	Chronic lymphatic leukemia, appendicitis
57.3	0.80	Endarteritis obliterans
56.5	0.50	Tuberculosis, mild arteriosclerosis
73.2	0.49	Three cases—lobular pneumonia; tuberculosis; chronic ulcerative colitis
53.3	1.06	Acute gangrenous vaginitis
64.6	0.58	Arteriolar nephrosclerosis (hypertension), slight arteriosclerosis of aorta
73.4	0.22	Astrocytoma of cerebellum
60.9	0.90	Arteriolar sclerosis, generalized arteriosclerosis
66.3	0.36	Acute bacterial endocarditis, generalized mild arteriosclerosis
72.1	0.60	Seven cases
63.9	0.56	
69.3	0.88	Rheumatic heart
60.0	0.54	Hypertension, generalized arteriosclerosis
68.4	0.65	Lobar pneumonia, medial calcification of aorta
72.2	0.67	Rheumatic endocarditis, generalized arteriosclerosis, moderate arteriolosclerosis
71.3	1.19	Carcinoma of colon, senile arteriosclerosis
70.2	0.89	Carcinoma of mouth
82.5	0.44	Purulent bronchitis, mild senile arteriosclerosis
63.8	0.61	Chronic nephritis and uremia, generalized arteriosclerosis, arteriolosclerosis
73.4	0.54	Carcinoma of colon, senile arteriosclerosis, hypertension
62.0	0.79	Cirrhosis of liver
67.9	1.05	Carcinoma of duodenum
70.0	1.05	Abscesses of liver, acute cholecystitis, acute cholelithiasis, medial calcification of aorta
69.3	0.73	
70.0	0.83	Astrocytoma of cerebellum
76.4	0.74	Pneumonia and appendicitis, carcinoma of stomach, mild arteriosclerosis
63.2	1.03	Carcinoma of ovary
75.8	0.66	Rheumatic endocarditis
71.6	0.97	Carcinoma of tongue, arteriosclerosis
67.1	1.30	Purulent bronchitis
75.2	0.63	Carcinoma of colon
67.4	1.15	Aplastic anemia, medial calcification of aorta
71.8	0.90	Aleukemic leukemia
67.5	1.63	Gallstones, jaundice, mild generalized senile arteriosclerosis
71.7	0.54	Adenoma of thyroid gland
72.5	1.77	Abscesses of liver, acute cholecystitis, acute cholelithiasis, medial calcification of aorta
70.6	1.24	Coronary sclerosis (advanced calcification)
62.6	1.01	Ulcer of stomach
72.9	1.25	Lobular pneumonia, generalized moderate arteriosclerosis
70.4	1.04	

COMMENT

The chief change in the pathologic material is an increase in the amount of the fatty extract, and particularly in the proportion of cholesterol to total fatty extract. This increase apparently becomes greater with increasing severity of the lesions rather than with increasing age. The table appears to show also that as the severity of the lesions increases, there is first an increase in the percentage of cholesterol esters in the fatty extract, and then, as the process continues, a decrease, but when the ester values were plotted against the fatty extract values, it was apparent that there was too much variation to permit any curve to be drawn. A similar curve drawn for free cholesterol showed, more definitely, a slight increase in the proportion of free cholesterol with increasing severity of the lesions. However, when the ratio of free to ester cholesterol was calculated, the changes were more striking. In the normal tissue the ratio of free to ester cholesterol decreases steadily with increasing age (from 4 for the youngest to 0.38 for the oldest aorta; average, 1). In the pathologic tissue this ratio apparently decreases up to a certain point and then rises quite definitely, so that in the late lesions the proportion of free to ester cholesterol is much greater than in the early lesions (the average ratio 1 in normal, 0.56 in early, 0.73 in medium, and 1.04 in late lesions). This was a surprise and contrary to Schönheimer's finding of a steadily increasing ratio of ester to free cholesterol with progressive pathologic changes. Our figures seem, then, to bear out more fully Aschoff's infiltration theory: that cholesterol esters along with other fats are laid down in the aorta from the blood—merely a physical deposition without any selective process on the part of the aorta. Later the cholesterol esters are split, leaving increasing amounts of free cholesterol.

The phospholipids remain practically constant in the three types of plaques and their average value (17 per cent of the total fatty extract) is much greater than that reported by Schönheimer for his series, but this is undoubtedly due to a difference in extraction. In a recently published paper on the analysis of alcoholic extracts of whole fixed aortas Lehnherr [7] reported phospholipid values similar to ours. Normal tissue from young aortas shows a higher phospholipid content than the damaged tissue shows, whereas normal tissue from two old aortas (aged 60) shows phospholipid values similar to those of the plaques and, at the same time, higher total cholesterol values than found for young normal tissue. This is interesting as a suggestion of the effect of age alone on the fat content of the aorta.

Some of the variations in our figures are undoubtedly due to the difficulty of an absolutely clean separation of the intimal tissue involved

7. Lehnherr, E.: New England J. Med. **208**:1307, 1933.

in lesions from the surrounding tissue, and also to the fact that any individual class of lesions appears to be influenced by the state of the aorta as a whole. For example, in several cases in which both early and late, or both medium and late lesions were taken from the same aorta the percentage of fatty extract and of total cholesterol in the early or medium lesions was above the average for the group, tending to approach the value found for the late lesions. It is interesting, too, that one case of hypertension and one of cholelithiasis showed abnormally high values for fatty extract.

SUMMARY

Analysis of arteriosclerotic plaques from forty-five human aortas showed a constant amount of phospholipids, an increase of total fatty extract and total cholesterol with increase in the severity of the lesions, and also an increase, in the late lesions, in the ratio of free to ester cholesterol.

Notes and News

University News, Promotions, Resignations, Appointments, etc.—William Bulloch has retired from the chair of bacteriology at the London Hospital Medical College. The title of emeritus professor of bacteriology has been conferred on Dr. Bulloch.

Arthur W. Wright has been appointed professor and head of the department of pathology at Albany Medical College to succeed Victor C. Jacobsen who has resigned.

Albert E. Casey, Rockefeller Institute for Medical Research, New York, has been appointed associate professor of pathology at the University of Virginia.

Harold W. Stewart has been made associate in pathology in Jefferson Medical College, Philadelphia.

Gene H. Kistler has been appointed associate professor in the department of pathology and bacteriology in the University of Alabama.

According to *Science* the 1934 James E. Stacy Award, consisting of a medal and a sum of money given by the faculty of medicine of the University of Cincinnati for significant contribution to the theory of focal infection in theory or practice, has been bestowed upon Dr. E. R. LeCount, professor of pathology in Rush Medical College, for "his experimental studies on the isolation of streptococci from sore throats and the experimental induction, through their injection, of acute, healing and scarring types of nephritis, identical with the chronic nephritides observed in man."

A grant of $1,000 has been made by the Simon Baruch Foundation for Medical Research to the pathologic laboratories of St. John's Hospital, Brooklyn, to carry forward an investigation by Theodore J. Curphey on the effect of extracts of fetal endocrine tissue on cell growth.

Herbert U. Williams, professor of pathology in the school of medicine, University of Buffalo, has retired after more than forty years of teaching. His address is 30 Arlington Place, Buffalo, N. Y.

Society News.—The forty-fifth annual meeting of the Association of American Medical Colleges will be held at Nashville, Tenn., Oct. 29, 30 and 31, 1934.

At the thirteenth annual convention of the American Society of Clinical Pathologists, held in Cleveland from June 7 to 11, the following officers were elected: president-elect, F. M. Johns, New Orleans; vice-president, B. S. Kline, Cleveland. The Ward-Burdick Medal was awarded to R. R. Kracke for his work on agranulocytic angina. Ludwig Hektoen and Otto Naegeli were elected honorary members.

The American Association for the Study of Neoplastic Diseases will hold its next meeting in Washington, D. C., on Sept. 6, 7 and 8, 1934, at the Mayflower Hotel.

Abstracts from Current Literature

Experimental Pathology and Pathologic Physiology

GROWTH INHIBITOR IN KIDNEY DESICCATES. F. A. MCJUNKIN and C. D. HARTMAN, Am. J. Path. **9**:739, 1933.

It is well known that certain organs elaborate chemical regulators, or hormones, which govern growth and metabolism. It has been demonstrated that several of these inhibit karyokinesis of the cells that produce them. This self-regulatory function of the hormones is not known to depend on their metabolic activity. In the case of the parathyroid gland, the hormone made inactive, so far as calcium metabolism is concerned, still inhibits proliferation of the parathyroid cells. The experiments recorded in this paper describe methods for the extraction from the rat's kidney of an inhibitor of renal tubule mitosis. It is not known that this inhibiting agent exercises any control over growth of the body as a whole, or that it plays any rôle in metabolism. Simple aqueous extracts made from the fresh macerated kidney had little influence on the proliferation of renal epithelium. Simple aqueous extracts of desiccated kidney, however, were inhibitory when sufficiently large doses were injected. A more satisfactory potency was obtained by means of acid-alcohol extraction of either fresh or desiccated kidney. The successful extracts were made with dilute acid and 60 per cent alcohol, and at temperatures of 40 C. or less. The acid-aqueous extracts that were tested were without effect on the renal epithelium. They were prepared at 70 C. or more, and the strength of acid was relatively high. Further attempts are being made to purify and concentrate the extract.

AUTHORS' DISCUSSION AND SUMMARY.

THE REACTION TO FINE AND MEDIUM-SIZED QUARTZ AND ALUMINUM OXIDE PARTICLES (SILICOTIC CIRRHOSIS OF THE LIVER). L. U. GARDNER and D. E. CUMMINGS, Am. J. Path. **9**:751, 1933.

Three series of rabbits were given intravenously 1.3 Gm., respectively, of silica particles 1 to 3 microns in diameter, silica particles 6 to 12 microns in diameter and aluminum oxide particles 1 to 3 microns in diameter. The injections were given in divided doses and required from one to four months for their completion. These particles were segregated in different locations according to their size. The largest ones were caught in the pulmonary capillaries, those of intermediate size in the spleen and hepatic lymph nodes, and the finest ones in the liver. The fine particles of silica were the most active and produced a progressive coarsely nodular cirrhosis of the liver attended by extensive destruction of the parenchyma, followed later by regeneration in certain areas. This cirrhosis was the result of a typical hyaline nodular silicotic fibrosis originating in the portal connective tissues. Coarse particles, 10 to 12 microns in diameter, were much less irritating. They excited a simple foreign body type of reaction which progressed very little in practically three years' time. Fine particles of aluminum oxide the same size as those of the smaller silica fraction and introduced in essentially the same quantity were merely phagocytosed and produced no fibrosis in the stroma of any organ where they were deposited. These observations support the point of view that the injury produced by silica is specific and chemical rather than physical.

AUTHORS' SUMMARY AND CONCLUSIONS.

PROLONGATION OF PREGNANCY IN THE RABBIT BY INDUCED OVULATION. F. F. SNYDER, Bull. Johns Hopkins Hosp. **54**:1, 1934.

The rôle of corpora lutea in parturition was studied by induction of ovulation during pregnancy with urine extract so that at term there was a fresh set of

corpora lutea at the stage of maximal activity. Under these conditions the following observations were made: Normal parturition at term was never observed; in most animals, pregnancy was prolonged, the onset of parturition being delayed until fifteen days after injection (i. e., the fortieth day) or until the end of the life span of the induced corpora lutea. Retention of postmature fetuses longer than the life span of the induced corpora lutea was associated with injury of the uterine wall. Solution of pituitary administered at term failed to induce parturition in a dosage one thousand times greater than the amount normally effective. Fetuses survived in the uterus three days past term, i. e., thirty-five days, and developed to excessive size. An estimate of the functional reserve of the placenta at term was afforded by the extent of the development of postmature fetuses and the persistence of glycogen in the placenta at forty-one days. By varying the stage of pregnancy at injection, the dosage and the parity of the animal, a method was found by which pregnancy was prolonged in twenty of the twenty-three animals, while abortion of the litter occurred in only three. In abortion the fetuses were expelled either alive or before any maceration had taken place. The abortions were limited in their occurrence to the second or the third day after injection. There was no support for the view that the onset of parturition is caused by changes in the fetus, senility of the placenta or mechanical distention of the uterus. Retention of the fetus in the uterus, in the rabbit at least, is under hormonal control. Termination of its retention coincides with termination of the life cycle of the corpus luteum.

AUTHOR'S SUMMARY.

EXPERIMENTAL EXOPHTHALMOS AND HYPERTHYROIDISM IN GUINEA-PIGS. H. B. FRIEDGOOD, Bull. Johns Hopkins Hosp. **54**:48, 1934.

Simultaneous studies of the basal metabolic rate and pathologic changes of the thyroid gland were carried out on thirty guinea-pigs given extracts of the anterior lobe of the pituitary gland over a period extending from forty-eight hours to one hundred and ninety days. Six guinea-pigs were used for controls. The available data suggest the following conclusions:

The injections produce a syndrome which is remarkably similar to that of exophthalmic goiter in man, but there is no evidence that the two conditions are identical in their pathogenesis.

The behavior of the basal metabolic rate during a prolonged period of injections is extremely variable. It is characterized by an initial increase followed by a spontaneous remission, and may exhibit subsequent recrudescences. The spontaneous remission in the basal metabolic rate may be due to a relative functional insufficiency of the thyroid gland (rapid depletion of the stored precursors of the calorigenic hormone with or without parenchymal injury), although the development of a protective "antipituitary" or "antithyroid" substance must be considered a possibility.

Parenchymal hypertrophy and hyperplasia of the thyroid gland appear simultaneously with systemic evidence of its hyperactivity, but these same pathologic changes may still be present when the basal metabolic rate is spontaneously decreasing. In the latter event, this pathologic picture is associated with a decreasing activity of the thyroid gland.

Exophthalmos is produced independently of the calorigenic hormone of the thyroid gland. Anterior pituitary extract seems to be more capable of inducing prominent exophthalmos in the absence of hyperthyroidism and in the presence of hypothyroidism. Chronic exophthalmos which persists after the injections are discontinued may result from prolonged administration of the extract.

AUTHOR'S SUMMARY.

THE NERVOUS SYSTEM IN DEFICIENCY DISEASES. H. M. ZIMMERMAN and E. BURACK, J. Exper. Med. **59**:21, 1934.

Adult dogs maintained on an artificial balanced ration adequate, so far as is known, in all dietary essentials except water-soluble, heat-stable vitamin B_2 (G)

presented, after a sufficient time, a slowly progressive disease characterized by loss of weight, persistent vomiting and diarrhea, and marked muscular weakness, which ended fatally in from two hundred to over three hundred days. The clinical features of this condition are quite different from those characterizing the canine disease known as black tongue. The anatomic changes consist of marked demyelinization of the peripheral nerves, including the vagus; degeneration of the medullary sheaths and replacement by gliosis of the posterior columns of the spinal cord, particularly the fasciculi graciles; degeneration of the medullary sheaths of the posterior and less often of the anterior nerve roots of the cord; occasionally slight degenerative changes in most of the other fiber tracts of the cord. Attention is called to the fact that degenerative lesions in the central nervous system similar to or identical with these have frequently been described in pellagra in man.

AUTHORS' SUMMARY AND CONCLUSIONS.

NUTRITIONAL MYOPATHY IN DUCKLINGS. A. M. PAPPENHEIMER and M. GOETTSCH, J. Exper. Med. **59**:35, 1934.

Ducklings fed on a diet of skimmed milk powder, casein, corn-starch, lard, cod liver oil, yeast, salts and paper pulp rapidly acquire a disease characterized by extreme and progressive myasthenia, ending in death within a few days. Pathologic changes are found in the skeletal muscles. These show widespread hyaline necrosis of fibers, with edema and cellular reaction. The brain and other parts of the central nervous system are not affected, and no significant alterations are found in other viscera or tissues. The creatine content of the muscles is reduced in proportion to their injury. Controls on a natural food diet remain free from the disease.

AUTHORS' CONCLUSIONS.

THE HYPOPHYSIS IN SO-CALLED CONSTITUTIONAL OBESITY. E. ZEYNEK, Frankfurt. Ztschr. f. Path. **44**:387, 1933.

In 81 per cent of thirty-two cases of obesity the hypophysis showed an absolute increase of the basophilic cells. The opinion is stated that the basophilic pituitary cells have a definite relation to the fat metabolism. This view is regarded as partly supported by the fact that in Cushing's syndrome of pituitary basophilism, obesity plays an outstanding part.

WILLIAM SAPHIR.

FUNCTIONAL DISTURBANCES OF THE PERIPHERAL CIRCULATION. B. FISCHER-WASELS, Frankfurt. Ztschr. f. Path. **45**:1, 1933.

In this article, which comprises the entire first part of this volume, Fischer-Wasels discusses the more important questions and the more modern researches in this field. Ricker's law of the circulation is rejected, and the belief is expressed that it is not a law but merely a rule. It is formulated in that a slight irritation produces, as a rule, an active hyperemia and acceleration of the current. A medium irritation produces, as a rule, a narrowing of the arterioles and a slowing of the circulation. A severe irritation produces, as a rule, a more marked slowing of the circulation, a maximum dilatation of the capillaries and stasis. He points out that the circulation may be impaired because of (1) hindrance of the currents of the blood, (2) damage of the blood corpuscles, (3) changes in the walls of blood vessels and (4) primary tissue changes resulting in local anemia and ischemia or in hyperemia combined with either slowing or increase of the circulation. He believes that spontaneous gangrene may occur without organic occlusion of the vessels. Such a gangrene may be the result of a primary hypersensitivity of the regional circulatory region which produces a standstill of the circulation under the influence of toxic substances or of locally formed metabolic products. The vasomotor nerves do not play a primary principal rôle in causing the gangrene. He stresses how important it is to be critical in the assumption that functional spasms of the vessels explain pathologic observations. Otherwise, much will be explained on the basis of

a hypothesis of arterial spasm. It is emphasized that spasm alone does not cause necrosis. The pathogenesis of brain hemorrhage is also discussed. There is primarily a destruction of brain tissue as a result either of trauma or of toxins (direct effect) or because of local circulatory disturbances (indirect effect). As a result of the primary destruction split products may be present which secondarily damage the walls of blood vessels either by accentuating the local disturbances of circulation or by producing anatomic changes of the vessels which finally may result in necrosis. The damage to the walls of the vessels may also cause reflectory disturbances. The result of the vessel changes may be one massive hemorrhage or multiple simultaneously occurring small hemorrhages. The value of motion pictures of the circulation is stressed.

O. SAPHIR.

Pathologic Anatomy

LIPOID HYPERPLASIA OF THE GALLBLADDER. J. BORENDES, Arch. f. klin. Chir. **175**:266, 1933.

One hundred and twenty-seven gallbladders that showed signs of lipoid infiltration were studied microscopically. No causative relationship was noted between the storage of the lipoid and gallstones. Nor was there evidence of a primary disturbance in cholesterol metabolism as a basis for lipoid infiltration. There was no connection between the storage of lipoid and inflammation. The accumulation of lipoids results from a deposit of cholesterol esters in the bile. On stagnation of lymph in the mucosa of the gallbladder the cholesterol esters are resorbed and deposited in the tissue.

JACOB KLEIN.

MULTIPLE CHYLOUS EFFUSION IN BILATERAL PULMONARY FIBROSIS. P. STEINER, Beitr. z. Klin. d. Tuberk. **81**:757, 1932.

Necropsy on a 32 year old woman who had died with signs and symptoms of cardiac insufficiency revealed chylous effusions into both pleural cavities, the peritoneum and the pericardium. No obstruction of the thoracic duct could be demonstrated. These findings are explained on the basis of an accompanying extensive pulmonary fibrosis with sclerosis of the pulmonary veins, marked congestion of the lesser circulation, obliteration of the pulmonary lymphatic circulation and fixed diaphragm. Three years previously the patient had had exudative pleurisy on the right side following influenzal bronchopneumonia, and a year later exudative pleurisy on the left side. Both healed by massive fibrosis progressively invading the lungs.

AARON EDWIN MARGULIS.

TUBERCULOSIS OF THE PERICARDIUM. ERNST KELLER, Beitr. z. Klin. d. Tuberk. **82**:213, 1933.

Tuberculous pericarditis was found in 130 of 15,659 autopsies in the pathological institute of the University of Heidelberg, an incidence of 0.9 per cent of the total and of 5 per cent of all persons dying of tuberculosis. The disease occurred twice as frequently in males as in females, but without predilection as to age. The associated tuberculosis was miliary and of a predominantly productive form in 12 per cent, and exudative in 88 per cent. The manner of infection of the pericardium was by continuity from lymph nodes and the pleura in 17 per cent, by lymphatic spread in 48 per cent and by hematogenous spread in 35 per cent.

AARON EDWIN MARGULIS.

ARGENTOPHILIC FIBERS IN THE PRIMARY COMPLEX OF TUBERCULOSIS. M. D. ARIEL, Beitr. z. Klin. d. Tuberk. **82**:341, 1933.

Ariel studied the histology of the primary complex in sections prepared by impregnation with silver. This method permits greater insight not only into the pathologic anatomy of the lesion but also into the evolution of the process. Forty

primary complexes were so studied, and a comparison of the development of the parenchymal lesion with that of the associated lesion in the lymph node was worked out. It was found that evidences of exacerbations were more frequent in the foci of lymph nodes, with concomitant earlier formation of granulation tissue. By contrast, the parenchymal lesions rarely showed evidence of exacerbations, and the circumfocal granulation tissue more commonly went on to organization and encapsulation.

AARON EDWIN MARGULIS.

LYMPHATIC CYSTS IN A HILAR GLAND. FRIEDRICH STEFFEN, Beitr. z. Klin. d. Tuberk. **82**:500, 1933.

Cystic transformation of the hilar and tracheobronchial glands, particularly of those at the bifurcation of the trachea, was found at necropsy in a patient with pneumonoconiosis. The cyst spaces were dilated lymphatic sinuses and lymphatic vessels. The cause was probably the impeded flow of lymph consequent to anthracosis of the lymph nodes. This is said to be the first observation of its kind reported.

AARON EDWIN MARGULIS.

THREE CASES OF MARKED CIRCUMSCRIBED ATROPHY OF THE LIVER. J. JESCHEK, Beitr. z. path. Anat. u. z. allg. Path. **89**:233, 1932.

Atrophy of one lobe of the liver with almost complete destruction of the parenchyma was found at autopsy in three women. In two of the women the finding was accidental and without relation to the cause of death, while in the other Banti's disease was diagnosed before death. The author regards the atrophy as a reparative stage of subacute yellow atrophy of the liver.

C. ALEXANDER HELLWIG.

MORPHOLOGIC EVIDENCE OF THE FUNCTIONAL STATE OF THE SUPRARENAL MEDULLA. M. STAEMMLER, Beitr. z. path. Anat. u. z. allg. Path. **91**:30, 1933.

By morphologic study of the medulla of the suprarenal gland in mice, rats and guinea-pigs after these had been subjected to a variety of experimental procedures that the physiologist has found to cause increased or decreased liberation of epinephrine Staemmler attempted to correlate the morphologic changes in the medulla with its functional state. Granting that the chromaffin substance bears a direct relation to the formation of epinephrine, he finds that the quantity of chromaffin substances does not give a true measure of the functional activity of the medulla. Vacuolation of the cells is of greater importance and indicates increased cellular activity and increased secretion. An increase in the chromaffin content may or may not be associated with vacuolation. The combination of poverty in chromaffin content and vacuolation is interpreted as evidence of hyperfunction and indicates both increased formation and increased liberation of epinephrine. Decrease in chromaffin substance without vacuolation may be due to increased liberation of epinephrine without increased secretion or to a primary disturbance of secretion. Either or both of these physiologic processes sooner or later lead to exhaustion of the medulla. The same physiologic process may yield evidence first of hyperactivity and then of exhaustion. The liberation of epinephrine is under the influence of the splanchnic nervous system, but the formation of epinephrine appears to be less definitely under nervous control. Morphologic evidence of hyperfunction was observed after unilateral extirpation of a suprarenal gland or ligation of its vein, after action of heat, after withdrawal of blood, and in the early stages of morphine, carbon monoxide and phosphorus poisoning. In these intoxications hyperactivity gave way to exhaustion. Peritonitis, diphtheria toxin and application of cold did not lead to increased secretory activity of the medulla. Liberation of the formed store of epinephrine was followed almost immediately by exhaustion.

O. T. SCHULTZ.

MASSIVE HEMORRHAGE FROM THE VESSELS OF THE NECK IN SCARLET FEVER. T. STEIN, Beitr. z. path. Anat. u. z. allg. Path. **91**:202, 1933.

Massive hemorrhage from the vessels of the neck is one of the rarer complications of scarlatina. In 630 cases of scarlet fever which came to necropsy in the Wassiljeostrow hospital for infectious diseases of children in Leningrad this complication was the cause of death 14 times. An additional case from another institution is included. In 10 instances the hemorrhage was arterial; in 8 of these a careful microscopic examination was made. In 5 instances the bleeding was of venous origin; a detailed histologic report of 4 of these is presented. Such hemorrhages are due to destruction of the wall of the vessel by necrosis or acute inflammation, the process reaching the wall from the adjacent diffusely inflamed tissues. In some instances the inflammatory process that encroached on the wall was gangrenous and appeared to be due to secondary invasion by fusiform bacteria; in other instances streptococci appeared to be the cause of the inflammatory process, which was then more purulent. The internal carotid artery was the site of rupture and hemorrhage in 3 cases; in these the phlegmon or abscess was retropharyngeal. The external carotid artery was involved in 1 case and the external maxillary artery in 2; in these the abscess was submaxillary. In 2 cases the common carotid artery, and in 3 the jugular vein, was the source of the hemorrhage, the abscess being situated in the lateral portion of the neck. Hemorrhage was from the anterior jugular vein in 2 instances; the abscess was situated in the anterior portion of the neck. In 2 cases in which the hemorrhage came from an ulcerated, necrotic lesion of the pharynx, the superior laryngeal artery was involved once and the ascending palatine artery once. In half the cases of arterial hemorrhage a single massive bleeding led immediately to death. In the other half the fatal massive bleeding was preceded by one or more smaller hemorrhages. The venous hemorrhages were usually multiple, and death occurred some hours after the terminal massive hemorrhage. In no instance did the fatal hemorrhage occur before the eighteenth or later than the thirty-fourth day of the disease.

O. T. SCHULTZ.

LAMBL'S EXCRESCENCES OF THE AORTIC VALVE. W. GÜNZEL, Beitr. z. path. Anat. u. z. allg. Path. **91**:305, 1933.

The minute excrescences of the ventricular surface of the segments of the aortic valve first described by Lambl in 1858 were found in 50 per cent of ninety consecutive necropsies. Their frequency increased with length of life. In twenty-six of the necropsies the excrescences were subjected to microscopic examination. They were composed of dense, avascular tissue, with no inflammatory cells or other evidence of inflammatory reaction. The collagen and elastic fibrils of the valve could be traced directly into the excrescence. These findings lead Günzel to deny the correctness of the two usually accepted views of the origin of the outgrowths: that they are organized small thrombi or that they are the result of subendocardial inflammation of the valve. He believes that their origin is purely mechanical and that they result from rupture of a few collagenic and elastic fibrils caused by the changes in pressure that occur with systole and diastole. The ruptured fibrils buckle outward and are then elongated into the typical excrescences by the continuing action of the blood stream.

O. T. SCHULTZ.

THE RETICULUM OF THE SPLEEN IN CIRRHOSIS OF THE LIVER. L. JORES, Beitr. z. path. Anat. u. z. allg. Path. **91**:343, 1933.

The reticulum of the spleen was studied by a modification of Leo Müller's method of preliminary digestion of paraffin sections by pancreatin. In central congestion of the liver of cardiac origin no increase of reticulum was detected,

but portions of individual fibers were thickened. In cirrhosis of the liver two types of alteration of the splenic reticulum were noted. In one there was periarterial and follicular fibrosis with hyperplasia of the sinusal reticulum. In the other the hyperplasia was limited to the pulp. The first type was associated with interlobular cirrhosis without jaundice and without hematogenous pigment in the liver; the second, with cirrhosis in which there were intralobular fibrosis and hematogenous pigmentation. The reticular hyperplasia of the spleen was often focal and unsymmetrical. The changes in the reticulum are ascribed to alterations in the function of the spleen.

O. T. SCHULTZ.

CHANGES IN THE KIDNEYS IN GOUT. T. FAHR, Centralbl. f. allg. Path. u. path. Anat. **57**:49, 1933.

Fahr reports the changes in the kidneys of a man, 74 years old, who had gout for thirty years and died of sclerosis of the coronary artery and heart failure. The kidneys weighed 60 Gm. each and were granular and gray-brown; the fat of the hilus was increased. The cortex was narrow. There were huge quantities of urates in the interstitial tissue of the medulla, and some smaller collections were separated by bridges of connective tissue. In seeking an explanation for this sharp localization of urates, Fahr considers first a hematogenous source. To reconcile this mode of transport with the localized deposition he believes that some special predisposition of the medulla is necessary, similar to that in the ear. As a second possibility, he considers that the urates may be carried in the lymphatics from the degenerated collecting tubules.

GEORGE RUKSTINAT.

THE EPITHELIUM OF THE PULMONARY ALVEOLI. F. ORSÓS, Centralbl. f. allg. Path. u. path. Anat. **57**:81, 1933.

Orsós believes that there is a continuous respiratory epithelium lining the alveoli. This is best studied in sections from 3 to 5 microns thick, allowing a view of the individual cells, or in sections from 50 to 200 microns thick, which convey the idea of a granular, fenestrated membrane. The cells comprising this structure are of varying types. One type is polygonal or rounded and has a large pale nucleus and radial striations in the periphery of the granular cytoplasm. Another has nuclear protoplasm, and another pseudopodium-like processes. Inclusions, such as coal pigment, drops of fat, masses of fibrin or red blood cells, frequently occur in the membrane. The membrane may be loosened during life by inflammation, as by an exudate under it. Postmortem hypostasis may similarly effect a separation. When the membrane is detached, it may imprison some air and in shrinking may resemble a punctured balloon. Further shrinking may result in a fine veil-like cellular mass. When the individual cells die they go over into the anuclear part of the membrane.

GEORGE RUKSTINAT.

MECKEL'S DIVERTICULUM AND GALLSTONES. H. HANKE, Centralbl. f. allg. Path. u. path. Anat. **57**:161, 1933.

Fifteen faceted gallstones, each about half as large as a pea, were found in a Meckel diverticulum in a man who had died of heart failure. The stalk of the diverticulum had a large lumen, and its lining had a fibrinopurulent coating. The gallbladder contained many stones, one the size of a hen's egg, and was chronically inflamed. The passage of stones from the gallbladder to the diverticulum was facilitated by an enlargement of the ductus choledochus and of the orifice of the diverticulum.

GEORGE RUKSTINAT.

HEMORRHAGIC INFARCTION OF BOTH SUPRARENAL GLANDS IN SEPSIS. S. SCHEIDEGGER, Centralbl. f. allg. Path. u. path. Anat. **57**:163, 1933.

A boy, 6½ years old, fell, striking his head on a stone. Meningitis developed within two days, and the boy died shortly after. The periosteum at the site of injury was intact, and there were slight evidences of meningitis. Both suprarenal glands contained free blood, especially in the medulla, and the capillaries contained emboli in which were diplococci and streptococci. Similar organisms were found in the cerebral exudate. Death was due to acute suprarenal insufficiency.

GEORGE RUKSTINAT.

AN UNUSUAL CAUSE OF SUDDEN DEATH IN SYPHILITIC AORTITIS. H. SIKL, Centralbl. f. allg. Path. u. path. Anat. **57**:228, 1933.

A tailor, 54 years old, died suddenly after complaining for a few hours of pain in the chest. At necropsy a fresh, clot-covered gumma was found at the mouth of the left coronary artery. Microscopically there were caseous necrosis of the media and thickening of the intima near the lesion. Spirochetes were found in the zone of acute inflammation, and there leukocytes were abundant.

GEORGE RUKSTINAT.

SPONTANEOUS RUPTURE OF THE GALLBLADDER IN SCARLET FEVER. H. SSAWRIMOWITSCH, Centralbl. f. allg. Path. u. path. Anat. **58**:49, 1933.

A tear 4 cm. long was found in the gallbladder of a boy, 6 years old, who died on the eighteenth day of scarlet fever. The gallbladder measured 12 by 4 cm., and the tear was on the left side of the fundus. There was no peritoneal reaction to the sterile bile, although rupture of the bladder had presumably occurred some days before death. At the edges of the rent were partially organized thrombi and hyperplastic epithelium. It is supposed that the rupture occurred in a markedly distended organ, because the latter was large, was not inflamed and was ruptured at the fundus. The overdistention is explained on the basis of paresis of the wall of the bladder due to toxemia. This, coupled with a slight mechanical obstruction to the outflow of bile, such as enlarged lymphatic glands about the duct or some dyskinetic alteration of the sphincter, might lead to rupture.

GEORGE RUKSTINAT.

A PERFORATING ANEURYSM OF THE LEFT VERTEBRAL ARTERY CAUSED BY GUMMATOUS DISEASE OF THE VASCULAR WALL. A. ESSER, Frankfurt. Ztschr. f. Path. **43**:448, 1932.

Autopsy of a woman whose condition had been diagnosed clinically as dementia paralytica revealed atrophy of the brain, a perforated aneurysm of the left vertebral artery, syphilitic aortitis and moderate sclerosis of the aorta. Histologic examination disclosed syphilitic meningo-encephalitis and gummas in the left vertebral artery. Esser discusses the etiology of the aneurysm and the differential diagnosis of syphilitic endarteritis and gummas of the walls of the blood vessels. Because the lesions were found in the intima and because giant cells were not present in them, it was at first difficult to decide whether they were gummas or whether they could be explained on the basis of a syphilitic endarteritis.

O. SAPHIR.

CONGENITAL AORTIC STENOSIS COMBINED WITH ENDOCARDIAL HYPERPLASIA IN THE NEW-BORN. E. DISSMAN, Frankfurt. Ztschr. f. Path. **43**:476, 1932.

A case is reported. The aortic valve in the region of the bulbus revealed three areas of thickening parallel to the aorta. One of the areas formed a ball-like structure measuring about 4 mm. in diameter, which almost completely obstructed the lumen of the aorta. The endocardium of the left ventricle correspond-

ing to the interventricular septum just beneath the aortic valve was white and measured as much as 2 mm. in thickness. Its surface was smooth in some portions and rough in others, resembling the trabeculation of the apex of the left ventricle. Dissman believes that the thickenings of the endocardium and in the region of the aortic valve were the result of primary hyperplasia of the embryonal texture of the valvular apparatus and of the endocardium. He does not believe that an intra-uterine inflammation was responsible for these changes.

O. SAPHIR.

HISTOLOGY OF THE INFLAMMATORY EXUDATE IN GRANULOCYTOPENIA ("AGRANULOCYTOSIS"). K. VAN DER WIELEN, Frankfurt. Ztschr. f. Path. **44**:34, 1932.

Eleven cases of granulocytopenia are described. The foci of inflammation revealed that the inflammatory cells corresponded to the cells of which the blood consisted in so far that in instances in which no granulocytes were present in the circulating blood polymorphonuclear leukocytes could not be demonstrated in the areas of inflammation, while in instances in which polymorphonuclear leukocytes were markedly reduced in number in the circulating blood, only a few were found in such areas. Many macrophages and a marked histiocytic reaction, however, could be demonstrated. Since the changes in the bone marrow were not uniform, so-called agranulocytosis does not seem to be a primary well characterized disease of the blood-forming marrow. There seems to be no connection between granulocytopenia and syphilis. Occasionally, however, antisyphilitic treatment may be of value. It is concluded that the dependence of the inflammatory exudate on the types of cells in the blood supports Fischer-Wasels' theory, according to which the leukocyte seen in areas of inflammation is an emigrated blood cell and not the product of local cell metamorphosis.

O. SAPHIR.

INFLUENCE OF ROENTGEN RAYS ON TRAUMATIC INFLAMMATION. H. BUHTZ, Frankfurt. Ztschr. f. Path. **44**:57, 1932.

Skin wounds treated with roentgen rays revealed twenty-four hours later a greater tendency toward healing than control wounds. One hour after roentgen treatment the migration of leukocytes in the region of the wounds was much more marked in the treated animals than in the nontreated controls. Four hours after treatment the maximum of the leukocyte migration was reached in the treated wounds. Twenty-four hours after treatment the accumulation of leukocytes was confined to the most superficial portions of the treated wounds, while hardly any leukocytes could be made out in the tissue surrounding these wounds. In the control wounds the peripheries showed a marked infiltration of leukocytes, which were also present a short distance away from the wounds. A transformation from connective tissue cells into leukocytes could not be demonstrated.

O. SAPHIR.

Pathologic Chemistry and Physics

STUDIES IN OSCILLOMETRY. ALFRED FRIEDLANDER, Am. Heart J. **9**:212, 1933.

The form of the oscillogram, taking curves of all extremities in each case, is of more importance than the estimation of the maximal oscillometric phase. The normal oscillogram may show definite variations in the maximal oscillometric phase (MOP) in the same patient at different times. This is dependent largely on the condition of peripheral resistance. Typical pathologic oscillograms are shown, demonstrating arterial thickening, essential hypertension with nephrosclerosis, and hypertensive heart disease with Mönckeberg's sclerosis. From the form of the oscillogram in typical cases definite conclusions may be drawn as to the condition of the vascular tree. Mixed forms of curve are often found. In such cases the oscillogram alone cannot afford a definitive diagnosis of the condition of the walls of vessels.

AUTHOR'S SUMMARY.

THE CREATINE CONTENT OF THE MYOCARDIUM OF NORMAL AND ABNORMAL HUMAN HEARTS. DONALD W. COWAN, Am. Heart J. **9**:378, 1934.

The average creatine content of the left ventricular myocardium as determined in forty-eight approximately normal human hearts was 194 mg. per hundred grams of tissue, this value being based on an arbitrary water content of 80 per cent. There were no differences in this creatine content related to either sex or age. A few hearts included in the normal group, but having creatine contents differing widely from the mean, are listed separately and the diagnoses given in detail. Analyses of seventeen decompensated hearts showed an average creatine content significantly lower than normal. Scar tissue was not a significant factor in producing this low value. Fifteen abnormal, but not decompensated, hearts had an average creatine content significantly lower than normal, but higher than the values for the decompensated hearts. These are listed separately, with their diagnoses given in detail. Septicemia *per se* had no effect on the creatine content of the left ventricle. An effect of hypertrophy *per se* on the creatine content of the heart was not definitely established. These findings suggest that the "reserve" of the heart closely parallels its creatine content.

AUTHOR'S SUMMARY.

BLOOD LIPIDS IN CHILDREN WITH SCARLET FEVER AND RHEUMATIC DISEASE. A. D. KAISER and M. S. GRAY, Am. J. Dis. Child. **47**:9, 1934.

Studies on the blood lipids of children with rheumatic disease and with scarlet fever revealed values similar to those found in normal children. The standard deviation from the mean was considerably greater in the children with these infections than in normal children. It is likely that the infection rather than the varied amount of fat ingested was responsible for the increased deviations.

STEATORRHEA IN PANCREATIC DISEASE AND SPRUE. JOSEPH H. PRATT, Am. J. M. Sc. **187**:222, 1934.

The fat content of dried feces was determined in thirty-three cases. In twenty-five cases the fat present constituted 30 per cent or more. In fifteen cases, 50 per cent or more of the dried feces was composed of fat. In these instances steatorrhea was due to obstructive jaundice, obstruction of the pancreatic ducts or sprue, except in three cases in which the cause of the fatty diarrhea was not discovered. The absorption of fat was studied in sixteen cases, the standard intestinal test diet of Adolf Schmidt being used. The fat lost in the feces ranged from 2.1 per cent in a patient with normal digestion to 66.2 per cent in a man with obstruction of the common bile duct and the pancreatic ducts. In the cases of steatorrhea, with two exceptions, 24 per cent or more of the fat of the food was excreted in the feces. The absorption of the nitrogen of the test diet was determined in this group of sixteen cases. In obstruction of the pancreatic ducts there was a loss of nitrogen in the stools, indicating faulty digestion and absorption of protein. When fat loss was due to absence of bile from the intestine the absorption of nitrogen remained normal. In sprue, the absorption of nitrogen is usually normal, but may be disturbed. The utilization of the starch in the food was normal in all the cases of steatorrhea studied. The chemical analysis of the feces for fat is important in determining, even approximately, the fat content of the stools, as the results of the microscopic examination of the fresh feces may be misleading. The determination of the percentage of nitrogen in the feces has proved of no value in diagnosis. To study adequately cases of fatty diarrhea it is necessary to determine the absorption of both nitrogen and fat with the patient on a weighed diet, preferably the standard intestinal test diet of Schmidt. Excluding the cases of steatorrhea due to absence of bile from the intestine, most of the instances studied in the present series have proved to be cases of sprue or pancreatic disease. In this study three cases of steatorrhea of unknown origin have been encountered. Further work is needed on similar cases. This should include, in addition to the

clinical study, a complete quantitative chemical analysis of the feces for the remains of food elements and the determination of the amounts of fat and nitrogen of the food that are lost in the stools, and finally a thorough study of the abdominal organs at autopsy.

AUTHOR'S SUMMARY.

COPPER AND IRON IN CELLULAR METABOLISM. A. LOCKE, D. O. ROBASH and L. E. SHINN, J. Infect. Dis. **54**:51, 1934.

A method is described for the approximation of that portion of the total amount of copper and iron present in tissue which may be presumed to be directly active in the motivation of cellular metabolism. Values are given for the copper and motivating iron contents of the tissues of the rapidly growing normal male rabbit which indicate the presence in the liver, heart, kidney and muscle of a metabolic catalyst containing two parts of reducing iron to each part of oxidizing copper. Approximately ten times as much of the catalyst may be present in the maximally active musculature of the heart as is present in the minimally used, least pigmented muscles of the thighs. The catalyst of the brain, orienting a metabolism more largely devoted to the support of respiration, may contain its active copper and motivating iron in a 1:1 ratio. Prolongation or intensification of the endogenous metabolism in the rabbit as the result of fasting, the feeding of thyroid, or fever is accompanied by a wasting of the tissues and a strain on the catalytic balances. Motivating iron is lost through oxidation, and the copper-ferrous iron ratio of the heart muscle may rise to values approaching those observed in brain. An identical effect is reached, with enormously greater rapidity, following injections of diphtheria toxin and following inoculation of Pneumococcus type I. The effect is not obtained in protected animals. The lowered metabolism and increased weakness and susceptibility to infection of rabbits maintained on cabbage are accompanied by a lowering of the copper levels. No specific changes in the copper and motivating iron contents of the tissues of the chicken accompany the growth of the Rous sarcoma. Changes are observed during the degeneration of the tumor. The metabolic catalyst of the tumor itself appears to contain less active copper per unit of active iron content than is present in the invaded tissue.

FROM AUTHORS' SUMMARY.

FURTHER OBSERVATIONS ON THE ELECTRIC CHARGE OF THE ERYTHROCYTES IN CERTAIN PROTOZOAL DISEASES. H. C. BROWN, Brit. J. Exper. Path. **14**:413, 1933.

It has been shown that the electric charge of the erythrocytes in malarial birds bears a definite relation to the degree of infection, and that the reduction in charge of the red cells of an infected bird is apparently an important factor in the extent to which phagocytosis takes place. In other words, when the bird with malaria shows a strong immunizing response in that it is successfully combating its infection, the negative charge of the red cells is considerably lowered, but in the bird in which the parasites continue to increase steadily the charge does not markedly differ from that of the red cells in a normal bird. This reduction in the negative charge of the red cells also takes place, but to a less extent, in the blood of mice recovering from Trypanosoma equiperdum infection, the change occurring at the time when antibodies appear in the peripheral blood. It has been shown that the reduction in the negative charge of the red cells is nonspecific, and due to the action of the euglobulin fraction of the serum on the erythrocytes concerned. It is well known that in phagocytosis of bacteria these enter the phagocytes when they have their negative charge reduced in the presence of a suitable electrolyte and immune serum. When one takes into account the protein changes in malaria, with the charge-reducing action of euglobulin, it seems conceivable that the rationale of the treatment of dementia paralytica by malaria might be the phagocytosis of the spirochetes induced by an increased euglobulin content of the patient's serum.

Caldwell, in discussing this subject ("Treatment of General Paralysis by Malaria"), stated that the improvement which takes place is primarily due to a destruction of the spirochetes, and has shown that not only the serum but also the cerebrospinal fluid of paralytic patients who have been treated with malaria shows a higher content of agglutinin for the spirochete than is shown by the serum or spinal fluid of untreated patients. If, then, the agglutination of the spirochete occurs during malaria therapy, it follows that the charge of the organism is lowered, and conditions are therefore more favorable for phagocytosis.

Although a considerable amount of work has been done on the sedimentation rate of the red blood corpuscles in various morbid conditions, no very definite explanation appears to have been given to account for the variations that occur. Jones concluded that either an increase of fibrinogen or a decrease in the ratio of albumin to globulin is responsible for an increased rate. It appears that in such diseases as kala-azar, malaria, syphilis and trypanosomiasis the electric charge of the red cell, and consequently the sedimentation rate, is dependent on the proportion of the various proteins present in the plasma, and that such changes in the protein composition of the cerebrospinal fluid are responsible for the lowering of the charge and consequent phagocytosis of the spirochetes in cases of dementia paralytica undergoing malaria therapy.

FROM AUTHOR'S DISCUSSION.

Microbiology and Parsitology

TYPHUS IN MICE. J. LAIGRET and J. JADIN, Arch. Inst. Pasteur de Tunis **21**:381, 1933.

Mexican virus transferred through mice by injecting brain containing it into their peritoneal cavities was successfully maintained for sixteen passages. Then the series was interrupted. Brain to brain passages were less successful, the virus failing after the fourth passage. With the human virus (Tunis) only several transfers were accomplished by either method of injection. Only silent infections appeared in all cases; the infections were made apparent by guinea-pig inoculations, but even in the guinea-pig controls latent infection was frequent. The survival of Mexican virus in mouse brains reached forty days with intraperitoneal injections, but only ten days with intracerebral injections.

M. S. MARSHALL.

STRUCTURE AND NATURE OF THE SO-CALLED PROTOZOAL BODIES IN THE EXCRETORY DUCTS OF THE SALIVARY GLANDS. G. C. PARENTI, Sperimentale, Arch. di biol. **11**:157, 1933.

The salivary glands of 200 persons, mostly children and fetuses, were examined microscopically. It was possible to demonstrate in 15 cases the protozoa-like cells in the excretory ducts. None were found in the salivary glands of adults. Parenti doubts that these are parasitic bodies, but believes rather that they are acinar cells which have assumed an atypical position and growth.

JACOB KLEIN.

BIOLOGY OF THE TUBERCLE BACILLUS. BRUNO LANGE, Beitr. z. Klin. d. Tuberk. **81**:235, 1932.

Lange reviews the newer work on the biology of the tubercle bacillus. He concludes that the greatest advances have been made in the technic of its isolation and culture and in appreciation of its virulence. He feels that little of the evidence relating to the supposed variation in form, filtrability and dissociation of the classic type is convincing. Restudy of the question of the pathogenicity of the bovine strain for man has reaffirmed that potentiality. He leans to the view that the most frequent way in which man in general is infected is by inhalation of few bacilli.

AARON EDWIN MARGULIS.

Immunology

SO-CALLED "THYMIC DEATH." G. L. WALBOTT, Am. J. Dis. Child. **47**:41, 1934.

Of a group of 102 cases in which the diagnosis of status thymicolymphaticus was made by various pathologists, 34 were selected in which no adequate cause of death had been determined. The remaining 68 cases were excluded, since other conditions, such as hyperthyroidism, trauma at birth, gastro-enteritis and respiratory infections, were associated with the lymphoid hyperplasia and in themselves were sufficient to cause death. In 11 of the 34 cases death occurred without previous illness, nor were there any pathologic lesions to indicate the presence of a previous illness. In 16 cases, minor, usually nonfatal incidents preceded death. In seven, a syndrome developed manifested as dyspnea, stridor, fever and shock. The lungs of all these patients presented uniform changes, characterized by capillary congestion, extravasation of blood cells and edematous fluid. These lesions alternated with areas of emphysema and atelectasis. In 17 cases petechial hemorrhages were present, involving the heart, pleura and lymph glands and various other viscera. In some, there were dilatation of the right side of the heart and degenerative changes in the liver and edema and capillary congestion in other organs than the lungs. Hypoplasia of the suprarenal glands and hyperplasia of the lymphoid organs, as noted by other authors, were present. Comparison of this pathologic process with that reported in anaphylactic shock in man reveals a close resemblance, if not a complete identity, of the two conditions. Eosinophilia of the tissues and an allergic familial or personal history point further to this conception. On the basis of these findings it is believed that death may be the result of a primary anaphylactic edema of the lungs and ensuing asphyxiation. Such a theory can be upheld only if one assumes (1) that anaphylactic shock may occur from incorporation into the body of nonprotein substances, and (2) that absorption of shock-producing antigen may take place by ways other than by injections. Evidence is presented both from personal experience and from that of others which tends to confirm these facts.

AUTHOR'S CONCLUSIONS.

PROTEINS AND AN ALCOHOL-PRECIPITABLE CARBOHYDRATE FRACTION OF GONOCOCCI AND MENINGOCOCCUS. A. K. BOOR and C. P. MILLER, J. Exper. Med. **59**:63 and 75, 1934.

No essential differences between the nucleoproteins and the intact cells of Gonococcus and Meningococcus were observed in their ability to engender immune substances (precipitins), to induce bacterial allergy in rabbits or to elicit cutaneous reactions (of the delayed type) in rabbits rendered hypersensitive to these organisms. Measured by their lethal action in mice, the toxicity of gonococcic and meningococcic nucleoproteins was found to be but slightly less than that of the intact cells. It seems probable, therefore, that the toxic action of these organisms is due chiefly or entirely to some constituent of the nucleoprotein. Extraction with acetone and ether in the cold did not reduce appreciably the toxicity of these organisms and their nucleoproteins, nor alter their immunologic behavior. Cross-precipitin reactions suggested that gonococcic nucleoprotein has an antigenic factor in common with the nonencapsulated pneumococcus cell, and meningococcic nucleoprotein, one in common with the capsular material of Pneumococcus type III. Tryptic digestion destroys these antigenic factors, but not those responsible for the cross reactions within the genus Gonococcus.

The alcohol-insoluble polysaccharides of Gonococcus and Meningococcus were found to contain 4.2 and 3.7 per cent nitrogen respectively, to be protein-free by chemical test, and to reduce Fehling-Benedict's solution only after hydrolysis. They were nontoxic for rabbits and mice and failed to engender antibodies (precipitins) in rabbits. They produced no cutaneous reactions in normal, snuffles-free rabbits, but caused typical allergic reactions of the delayed type in rabbits rendered hypersensitive to these organisms. Both carbohydrates reacted in high dilution with

antipneumococcus serum type III. For comparison, carbohydrates were prepared also from Micrococcus catarrhalis, Streptococcus haemolyticus, Staphylococcus aureus and a rough strain of Pneumococcus.

AUTHORS' SUMMARIES.

THE STUDY OF ANAPHYLACTIC PHENOMENA WITH BLOOD VESSEL PREPARATIONS. J. WEISSFEILER, Ztschr. f. Immunitätsforsch. u. exper. Therap. **79**:452, 1933.

Friedberger advocated the humoral nature of the anaphylactic reactions. Kritschewsky and others who propounded their cellular nature showed that thoroughly washed blood vessel preparations from sensitized animals continued to react to added antigen. That experiment of Kritschewsky was explained by Friedberger as being due to edematous fluid in the wall of the blood vessel and therefore not contradicting the humoral hypothesis. When the preparation is left hanging for from twelve to twenty-four hours, during which time the edema disappears, no reaction occurs when an antigen is introduced. Kritschewsky countered with an experiment which favors the cellular hypothesis: The failure of the blood vessel preparation to react after a long period is due not to the disappearance of the edematous fluid, but to necrobiotic changes. Weissfeiler repeated and confirmed the experiment of Kritschewsky and his associates. A comparison of the reactions of blood vessel preparations of guinea-pigs with those of rabbit's ear showed qualitative as well as quantitative differences. The preparations from the rabbit reacted irregularly and could be desensitized only after repeated additions of the antigen. According to Weissfeiler, the anaphylactic reaction results from a specific rise of an already normally present nonspecific sensitiveness toward the antigen.

I. DAVIDSOHN.

THE CURABILITY OF LATE SYHILIS IN RABBITS AND THE QUESTION OF IMMUNITY. P. MANTEUFEL and K. HERZBERG, Ztschr. f. Immunitätsforsch. u. exper. Therap. **79**:482, 1933.

Two groups of twenty rabbits were used for the experiment; one group had had a syphilitic infection, and the other, an infection with frambesia tropica. A reinfection with the homologous parasites was asymptomatic. Several months after the reinfection the animals were subjected to a thorough treatment with neoarsphenamine. The effect of the treatment was checked by means of glandular transplants which were negative in the cases tested. The rabbits were then reinfected for the third (or in some rabbits for the second) time. The infection was again asymptomatic. Five months later the rabbits were killed and their organs transplanted into the testicles of healthy rabbits. Only twenty-one rabbits survived the entire experiment, and the organs of thirteen of these were free from spirochetes, while the remaining eight still showed the presence of the disease. The thirteen rabbits were considered as immune by Manteufel and Herzberg. That interpretation is contrary to both hypotheses of Kolle, who maintains: (1) that late syphilis in rabbits cannot be cured with arsphenamine, and (2) that in syphilis of rabbits there develops only a "mono-immunity" against the homologous strain as contrasted with the panimmunity which develops in human syphilis. Cross-experiments failed to furnish a means of biologic differentiation between Spirochaeta pallida and Spirochaeta pertenuis.

I. DAVIDSOHN.

IMMUNITY IN SYPHILIS OF RABBITS. H. GROSSMANN, Ztschr. f. Immunitätsforsch. u. exper. Therap. **79**:495, 1933.

Twenty-seven rabbits with late syphilis received a course of three injections of neoarsphenamine (0.15 Gm. per kilogram of body weight) and were reinfected after twenty-nine days. Only one animal responded with a local reaction; in the others the infection was asymptomatic. The majority of the animals with asymptomatic infection (eighteen of twenty-three) were free from spirochetes, as shown by transplantation of their organs into healthy rabbits. From the result Grossmann

concluded an immunity existed in late syphilis of rabbits following the treatment with neoarsphenamine. The immunity was of short duration (less than five and one-half months). During the period of absolute immunity the skin of the rabbits was refractory to reinfection with Spirochaeta pallida. That observation invalidates, according to Grossmann, the prevalent opinion that cutaneous resistance (anergy) indicates the presence of spirochetes in such rabbits or, in other words, the incurability of late syphilis in these animals.

I. DAVIDSOHN.

RELATION BETWEEN FOOD AND IMMUNE HEMOLYSIS IN RATS. ARNE FORSSBERG, Ztschr. f. Immunitätsforsch. u. exper. Therap. **80**:16, 1933.

Lack of vitamin A had a slight depressing effect on the production of antisheep hemolysins in rats. No such influence was noticed when the other vitamins were removed. An increase of fat in the food had a depressing effect on the production of hemolysins. A similar effect followed the replacement of casein by gelatin and a decrease of protein in the diet. The cholesterol in the blood was inversely proportionate to the antibody titers. The antibody titer rose in response to feeding with lecithin and still more to feeding with choline, which may be the responsible fraction in the lecithin.

I. DAVIDSOHN.

A CRITICISM OF THE PHAGOCYTIC DOCTRINE. I. L. KRITSCHEWSKI and W. W. AWRECH, Ztschr. f. Immunitätsforsch. u. exper. Therap. **80**:28, 1933.

Metchnikoff postulated a greater potency of phagocytes in immune animals, but he never proved it experimentally. Many investigators after Metchnikoff tried to furnish the experimental evidence and thought that they had succeeded. Kritschewski and Awrech analyze their records and disagree with the conclusions. Their own experiments on phagocytosis in mice immunized with Spirillum Duttoni failed to show any evidence of an increase of phagocytic activity in vitro and in vivo as compared with nontreated animals.

I. DAVIDSOHN.

THE PHENOMENON OF PLASMA COAGULATION IN STAPHYLOCOCCIC INFECTIONS. MARIA SUDHUES and R. SCHIMRIGK, Ztschr. f. Immunitätsforsch. u. exper. Therap. **80**:42, 1933.

The ability of staphylococci to coagulate human plasma was not influenced by the presence of acute or chronic staphylococcic infections. Similar results were obtained with rabbits infected with virulent staphylococci. The differences in the coagulation of plasma due to the action of staphylococci are not due to antibodies directed against the staphylococci but are probably caused by chemical properties of the plasma. The rapidity of the coagulation of the plasma was inhibited by the addition of bile salts and of lecithin.

I. DAVIDSOHN.

COAGULATION OF FIBRINOGEN AND "PSEUDO-AGGLUTINATION." IVAN GYOERFFY, Ztschr. f. Immunitätsforsch. u. exper. Therap. **80**:52, 1933.

Bordet and Streng described the phenomenon of conglutination of red blood cells by active ox serum. They attributed it to a special substance in the ox serum which they named "conglutinin." Streng described the same phenomenon in mixtures of certain bacterial species with active ox serum. In a previous report Gyoerffy proved that the phenomenon of conglutination of red blood cells can be satisfactorily explained without the aid of a new immunologic substance (conglutinin): The active ox serum hemolyzes the red blood cells, and during hemolysis, a ferment (kinase) is liberated which brings about flocculation of the residual fibrinogen in the ox serum. In the present report, Gyoerffy shows the validity of the same explanation for the phenomenon of flocculation in mixtures of bacterial suspensions and active ox serum. Flocculation took place only when the ox serum had normal lysine for the bacteria present in the mixture. Extracts

of bacterial bodies were flocculated. Serums of dogs, guinea-pigs and cats were not suited for the experiment. According to Gyoerffy, the results disprove the conglutination hypothesis of Bordet and Streng.

I. DAVIDSOHN.

Tumors

SARCOMATOID METASTASES IN THE LYMPH NODES DRAINING A PRIMARY CARCINOMA WITH A SARCOMATOID STROMA. R. B. GREENBLATT, Am. J. Path. **9**:225, 1923.

A case of sarcomatoid metastases in lymph nodes draining a primary carcinoma with a sarcomatoid stroma is reported. The usefulness of Masson's trichrome blue stain, particularly in the histologic study of the fibroglia of fibroblasts, is emphasized. The possibility of epithelial metaplasia is discussed. An analogy between this case and the experimental tumors of Ehrlich, Haaland and others is assumed. The dividing line between mixed tumors and tumors the stroma of which is not clearly neoplastic is difficult to determine. In this case further metastases by way of the blood stream alone will decide. The occurrence of sarcoma in the lymph nodes may be explained on the basis of the absorption of products from the degenerated epithelium by the lymphatics. This initiates a reaction of the stroma in the lymph nodes which may become neoplastic, depending on the tissue response of the host and the irritative quality of the products liberated by the degenerating cancer cells.

AUTHOR'S SUMMARY.

NEUROBLASTOMA METASTASES IN BONES, WITH A CRITICISM OF EWING'S ENDOTHELIOMA. H. C. COLVILLE and R. A. WILLIS, Am. J. Path. **9**:421, 1933.

A tumor presenting all the accepted characteristics of Ewing's sarcoma of bone was shown at autopsy to be one of many metastases from a suprarenal neuroblastoma. A review of certain adequately recorded cases of supposed multiple bone sarcoma that came to autopsy leads to the conclusion that these also were instances of suprarenal neuroblastoma with skeletal metastases. The term "Ewing's sarcoma," while possessing clinical value as defining a syndrome presented by a certain group of tumors affecting bones, has no established claim as designating a pathologic entity. It is not denied that there may be a primary bone tumor presenting the Ewing syndrome, but it is believed that further study will disclose the metastatic nature of most of the tumors with this syndrome, and it is strongly suspected that in many of the cases the primary growth will prove to be a suprarenal neuroblastoma.

AUTHORS' SUMMARY.

CALCIFIED EPITHELIOMA OF THE SKIN. K. CH'IN, Am. J. Path. **9**:497, 1933.

Ten cases of calcified epithelioma of the skin examined in the pathologic laboratory of the Peiping Union Medical College are reported. Tumors of this type form a distinct group of neoplasms that are anatomically and clinically well defined. They are circumscribed, well encapsulated growths beneath the skin, consisting of lobulated epithelial masses with a network of usually hyalinized fibrous stroma. The epithelial cells are small, oval, deep-staining and closely packed, and have a marked tendency to undergo necrosis, calcification and ossification. A study of the 10 cases and the 116 instances collected from the literature indicates that the growths are distributed most frequently on the head and neck and occur usually in younger persons. The large majority of the tumors are benign, but a few cases of recurrence following removal have been recorded.

AUTHOR'S SUMMARY.

ANAPHYLACTIC MANIFESTATIONS IN CANCER. M. CUTLER and W. SAPHIR, J. Allergy **4**:389, 1933.

An investigation was made to determine whether cancer produces anaphylactic phenomena. A study of this kind seemed warranted in view of the old clinical observation that many patients with cancer suffer frequently from the so-called anaphylactic diseases, such as hay fever, bronchial asthma, urticaria, angioneurotic edema and vasomotor cutaneous disturbances. Furthermore, there was reason to expect the presence of an anaphylactic condition in the human being with carcinoma since similar conditions have been reported in animals harboring malignant tumors. Two methods of approach were used. First, a search was made for local anaphylaxis. Skin tests with a cancer extract were made on sixty patients. Positive reactions were noted in 62 per cent of the patients with cancer as compared with 24 per cent of the controls. Second, an attempt was made to demonstrate anaphylactic antibodies in the serum of the patients with cancer who showed positive reactions to skin tests. Guinea-pigs previously sensitized with patients' serum were given injections of the cancer extract. These tests gave negative results.

W. SAPHIR.

MULTIPLE PRIMARY MALIGNANT NEOPLASMS. H. H. HURT and A. C. BRODERS, J. Lab. & Clin. Med. **18**:765, 1933.

Persons with malignant conditions are likely to have more primary malignant neoplasms than a review of the literature would lead one to believe. Multiple primary malignant neoplasm occurs most commonly in the same organ or in organs of the same system. Of the patients with malignant neoplasms seen at the Mayo Clinic in one year, 3.4 per cent had more than one primary malignant neoplasm. Reasons have been presented to show that the percentage is even higher. From the study of cases of multiple malignant neoplasm it seems that the factors which cause the development of the tumors also express themselves in the grade of malignancy of the tumors. A large percentage of patients with multiple primary malignant neoplasm give histories indicating that other members of the family have had malignant tumors. No conclusion as to the occurrence of multiple malignant neoplasm with reference to sex could be drawn. In this series, the average age at which the growths developed was 50.4 years. Seventy-one cases of multiple primary malignant neoplasm have been described in the literature.

AUTHORS' SUMMARY.

SWEAT GLAND CANCER OF THE BREAST. B. J. LEE, G. T. PACK and I. SCHARNAGEL, Surg., Gynec. & Obst. **56**:975, 1933.

The human breast develops as a modified apocrine sweat gland. Apparent sweat gland tubules and cysts occur in the normal adult breast, where they anastomose with the interlobular lacteal ducts. The characteristic features which distinguish the mammary sweat gland tubules from the lacteal ducts are: constant eosinophilia of the cytoplasm, an inner layer of high columnar cells, the occasional presence of myo-epithelial cells surrounding the tubules and the tendency to form intratubular and intracystic papillary tufts. The anatomic and staining characteristics of these cells persist through all the transitional phases of normal sweat gland tubules, cysts, intracystic papillomas, adenomas and carcinomas. Evidence is presented to substantiate the theory that sweat gland carcinomas of the breast may develop from preexisting sweat gland tubules, cysts and papillary adenomas. The various stages in this transition have been seen. Except for the peculiar properties of sweat gland structures in the breast which have been enumerated, the sweat gland carcinomas of the breast have much the same structure as other mammary cancers; e. g., one finds that the bulky adenocarcinomas, the comedocarcinomas, the papillary, intraductal and intracystic carcinomas, the medullary carcinomas, the carcinoma simplex and even scirrhous carcinoma of the breast are

represented in this group. Sweat gland cancers of the breast occur more frequently in swarthy brunettes, whose skin has large-pored, oily, coarse texture. Their regional distribution is mostly on the periphery of the breast, particularly in the axillary tail and submammary fold. The frequency of pain, adherence of the skin and ulceration are significant clinical features of sweat gland cancer of the breast. The degree of malignancy and the prognosis following treatment are practically the same as for the general group of mammary cancers. AUTHORS' SUMMARY.

Technical

SEDIMENTATION OF THE BLOOD IN SCHIZOPHRENIA. H. FREEMAN, Arch. Neurol. & Psychiat. **30**:1298, 1933.

Freeman studied by the method of Rourke and Ernstene the sedimentation test in fifty normal persons and forty-seven carefully selected patients with schizophrenia without visceral or other organic complication. He found that in schizophrenia the sedimentation rate was not higher than in the controls, regardless of the subtypes of this mental disorder, the length of hospitalization, the degree of mental deterioration, the content of sugar, cholesterol or nonprotein nitrogen in the blood, the blood volume, the total leukocyte count and numerous other factors.

GEORGE B. HASSIN.

DIAGNOSIS OF SYPHILIS FROM A DRIED DROP OF BLOOD. ALEJANDRO CHEDIAK, Arch. de med. inf. **1**:3 and 125, 1932. P. DAHR, Deutsche med. Wchnschr. **60**: 94, 1934.

The first paper of Chediak was a preliminary report; the second contains the technical details. A drop of capillary blood from the ear or finger is obtained on a glass slide. It is immediately defibrinated by stirring and permitted to dry. The test is best made soon after the blood has dried, but delays of a few days do not interfere with the test. To the dried defibrinated blood is added 0.015 cc. of a solution containing 3.5 per cent sodium chloride and 0.3 per cent sodium carbonate. The mixture is then transferred to another slide within a paraffin ring. The commercial clearing extract for the Meinicke test (M.K.R.) and the already mentioned salt solution are heated separately at 56 C. and then mixed in the proportions of 1:10. Of the mixture, 0.03 cc. is added to the blood. The slide is then shaken for three minutes and kept for thirty minutes in the moist chamber. If the reaction is strongly positive, the reading can be made after ten minutes. When viewed with the microscope, negative tests show brown granules; positive tests, a coarse black precipitate. A comparison was carried out with the Wassermann test (Noguchi antigen), the Kahn test and the clearing test of Meinicke. In a series of 1,005 cases, the Wassermann test was positive in 88 per cent, the Kahn test in 94 per cent, the Meinicke test in 92 per cent and Chediak's test in 86 per cent. The intensity of the precipitate permits a quantitative estimation which compares well with that in the other tests. Chediak's method was checked by Dahr on 600 subjects. Of the 475 who had given negative reactions to other tests, 467 gave negative reactions to the Chediak test, and 8, or 1.7 per cent, falsely positive reactions. Of the 125 who had given positive reactions, 112, or 91 per cent, gave positive reactions to the Chediak test.

I. DAVIDSOHN.

PRELIMINARY TEST IN TRANSFUSION. O. THOMSEN, Klin. Wchnschr. **12**:1801, 1933.

Tube 1 receives six drops of serum from the recipient and one drop of a suspension of two drops of the donor's blood in ten drops of salt solution. The tube is placed in a water bath at 37 C., and if lysis occurs after from fifteen to thirty minutes the bloods are absolutely incompatible.

Tube 2 receives two drops of the recipient's serum, six drops of salt solution and one drop of the suspension of the donor's blood. In this mixture watch for agglutination.

If no lysis develops in tube 1 and no agglutination in tube 2, the donor is either of the same group as the recipient or a "universal donor." In this preliminary test it is essential that the serum of the recipient be free from all trace of lysis before the donor's blood is added.

STAINING OF PROTEIN-LIPOID COMBINATIONS BY SUDAN III. J. GOLDMANN, Virchows Arch. f. path. Anat. **290**:717, 1933.

Variations in the sudan III staining method reveal variable amounts of lipoid in the tissue. A combination of sudan III with alpha-naphthol brings to view a larger quantity of stained material than any other method. It stains the lipoid granules normally present in the polymorphonuclear leukocyte; the staining of these granules furnishes a criterion of the completeness of sudan III staining. Infiltrative lipoid as well as the "integral" lipoid of the lipoid-protein complexes of the protoplasm is stained by this method.

O. T. SCHULTZ.

IMPROVED TECHNIC FOR THE ASHING OF TISSUE SECTIONS. C. HACKMANN, Virchows Arch. f. path. Anat. **290**:749, 1933.

In Hackmann's modification of the Schultz-Brauns method for the preparation of ashed tissue sections, thin pieces of tissue are fixed for eight or ten days in formaldehyde vapor in a desiccator that contains a dish of calcium chloride. The sections are cut on the freezing microtome, those for the usual staining procedure being placed in water. The sections for ashing are placed in a dish of paraffin oil, from which they are floated to a slide to which a thin layer of gelatin has been applied. The oil is drained off, and the sections may be kept in a dust-free place until a convenient time for ashing. The heating should be gradual, and ashing should be done at a temperature of 350 and not over 400 C. Recognition of the nature and localization of the mineral salts in the ashed sections is facilitated by treating the latter with bromthymol blue, bromcresol purple and bromphenol blue.

O. T. SCHULTZ.

Society Transactions

PHILADELPHIA PATHOLOGICAL SOCIETY

Regular Meeting, Feb. 8, 1934

MORTON MCCUTCHEON, *President, in the Chair*

GRANULOSA CELL TUMOR. HENRY K. SEELAUS.

Robert Meyer states that there are three types of ovarian tumors which exert a hormonal effect, viz., the dysgerminoma and the arrhenoblastoma, along the lines of masculinization, and the granulosa cell tumor, along the lines of feminization. This report places on record the case of a married woman, aged 74. She had had the menopause twenty years before. Fifteen years later she had a return of the menses, which recurred regularly every twenty-eight days and lasted for three or four days. Nothing unusual was noticed about the pelvis until three months before her admission to the hospital, when a large mass was detected which, at operation, was found to be a tumor of the left ovary weighing 1,622 Gm. and measuring 19 by 15 by 10 cm. Microscopic study of the solid portions of the tumor revealed the tissue to be composed of a very cellular ovarian stroma with numerous small collections of epithelial cells, in some instances forming solid clumps and in other instances arranged around the margin of a lumen-like space. The cells and their arrangement very closely resembled graafian follicles. While this type of tumor is usually classified as malignant there was, in the sections examined, nothing in the surrounding tissue to indicate definite infiltration by the type of epithelium which formed the greater portion of the growth. To date, which is more than six months since the operation, there is no evidence of recurrence and all vaginal bleeding has ceased.

CONGENITAL HYPOPLASIA OF ONE KIDNEY ASSOCIATED WITH MALIGNANT HYPERTENSION. JOHN W. PARSONS.

A 14 year old white girl who was admitted to the hospital of the University of Pennsylvania in September, 1933, complained of severe headache, constipation, and pain in the right lower quadrant of the abdomen. She had been poorly developed all her life though mentally precocious. Two years before her admission she first noticed headaches which had recurred at irregular intervals since. Two months before admission abdominal pain suggested the diagnosis of acute appendicitis, but operation was deferred because of hypertension. On admission she was found to be markedly emaciated and to have extreme hypertension: 220 systolic and 175 diastolic. The fundus of each eye exhibited exudates and choking of the optic disk. The urine showed albumin, occasional casts and three or four white blood cells per high power field. The heart was not appreciably enlarged nor was there demonstrable peripheral arteriosclerosis. The patient's course was steadily retrogressive with headache and increasing visual disturbances leading to partial blindness. A subtemporal decompression was made in an effort to relieve the headaches but with only temporary success. The patient died four months after admission with signs indicating intracranial hemorrhage.

Autopsy revealed the right kidney to be about the size of a man's thumb, measuring 5 by 3 by 2 cm. and weighing 30 Gm. Its capsule was dense, and when stripped off it left a finely granular, dark red surface on which projected a large nodule of paler tissue which occupied the midportion of the organ. The poles of the kidney were fluctuant to palpation, and section revealed them to be dilated as by hydronephrosis, the wall being a dusky red and measuring 4 mm. in thick-

ness. The nodule in the midportion resembled a segment of normally formed, though sclerotic, renal tissue. The pelvis and the ureter were of normal size and showed no abnormality. The renal artery and vein were somewhat smaller than normal though in the usual position.

The left kidney was large, weighing 150 Gm. and measuring 10 by 6 by 3.5 cm. It was moderately sclerotic. The general structure was normal. The blood vessels, pelvis and ureter showed no abnormality. The urinary bladder was of the usual size, with slightly hypertrophied walls. The urethra was normal. The internal genitalia were infantile in size though of normal structure.

The heart was small with slight left ventricular hypertrophy. The brain was edematous and there was a massive recent hemorrhage in the temporal lobe as well as a smaller, older hemorrhage in the left putamen and the surrounding area.

Histologic examination of the left kidney revealed an occasional glomerulus containing small areas of necrosis within the capillary tuft with, otherwise, no glomerular changes. The tubules were moderately atrophic. The afferent arterioles showed marked hyaline degeneration with occasional necrotic arterioles. The small arteries showed moderate fibrous thickening.

Sections of the large nodule in the right kidney revealed changes similar to those in the left kidney. The thinned-out portions at the poles showed several peculiarities of structure. There were areas in which tubules filled with deeply eosinophilic hyaline material abounded, but in which there were no glomeruli. Other regions showed glomeruli and tubules of the highly cellular character and immature form seen in fetal kidneys while still other areas showed extensive hyalinization of closely packed small glomeruli. All of these regions were densely infiltrated by fibrous tissue. The mucosa lining the calices was hyperplastic, and the submucosa was richly infiltrated by lymphocytes and large mononuclear cells.

The changes in the left kidney and a part of the right kidney conform to the criteria for the diagnosis of malignant nephrosclerosis. Other areas in the right kidney were characteristic of congenital hypoplasia.

The case is presented to draw attention to the occurrence of juvenile malignant nephrosclerosis in a child having a congenital defect of one kidney.

MELANOMA WITH WIDESPREAD METASTASIS. MAX M. STRUMIA.

A white woman, 63 years old, applied Aug. 1, 1933, to her family physician for treatment of a lesion of the nail and nail bed of the index finger of the right hand, which appeared black and ulcerated (melanotic whitlow of Hutchinson). The physician fulgurated the lesion on several occasions. The patient applied for treatment at the Bryn Mawr Hospital on September 4. At this time the index finger of the right hand showed swelling of the dorsal surface of the distal phalanx, with ulceration measuring 20 by 20 by 8 mm. The nail and the nail bed were destroyed, and the borders of the ulcer were dark brown and firm. The finger was immediately removed at the basal joint, and microscopic examination of the lesion showed thickened, stratified squamous epithelium which dipped down into the subdermal structure, where epithelial pearls were present. Between the delicate strands of stratified squamous epithelium masses of cells were seen containing a large amount of melanin. A diagnosis of melanoma was made, and the patient was discharged.

Jan. 3, 1934, the patient was readmitted moribund and died in a few hours. At autopsy metastases were found in the skin, thyroid gland, mediastinal tissue and mediastinal lymph nodes, breasts, lungs and pleura, pericardium, cardiac muscle, diaphragm, surface of the peritoneum, mucosa of the ileum and colon, spleen and supplementary spleen, kidneys, liver, iliac nerve plexus, psoas muscle, bones, uterus, tubes and ovaries and also a few nodes in an old pedunculated fibroid of the uterus. The suprarenal glands weighed a little over 50 Gm. each and were entirely destroyed by pigmented tumor. The marrow of the rib as well as that of the sternum appeared completely black. Smears of marrow from the rib showed extremely few myeloid elements and nucleated red cells but a very large number

of hemohistioblasts (reticulo-endothelial cells) loaded with black pigment. This probably represented a blockage of these cells by the circulating pigment liberated by breaking down of the tumor cells. The fluid blood from the heart showed extremely few leukocytes, and very few were found in any of the vessels on section or in the various areas of inflammation following breaking down of the tumor. It is interesting that notwithstanding the complete breaking down of the suprarenal glands, the blood pressure was 220 systolic just before death and the blood sugar 35 mg. per hundred cubic centimeters of blood. The urine did not show melanotic pigment. Microscopic examination of the various organs revealed that all of the metastases were pigmented but that very few of the tumor cells were well preserved. These were always at the periphery of the nodes and occurred as polyhedral or elongated cells, lying irregularly, with large vesicular nuclei and in all cases with cytoplasm so filled with melanin as to obliterate almost completely every detail of the cell. It is of interest that the best preserved tumor cells were found in the atrophic uterus and the partly calcified fibroid of the uterus, where obviously the blood supply was very scanty.

GENERALIZED TORULOSIS ASSOCIATED WITH HODGKIN'S DISEASE. FRED D. WEIDMAN.

This article appears in full in this issue of the ARCHIVES, p. 227.

EXPERIMENTS ON TUMORS OF THE FROG. BALDUIN LUCKÉ.

In a recent communication (Lucké, Balduin: *Am. J. Cancer* **29**: 379, 1934) there has been described a cancerous disease of the common leopard frog. This disease is characterized by the occurrence of a single or multiple whitish tumor usually confined to the kidneys but in four instances of the present series extending to the extrarenal retroperitoneal tissue. The new growths vary in size from small whitish nodules to a mass weighing ten times more than the normal kidney. Microscopically the tumors have the appearance of richly cellular adenocarcinoma. Unlike human adenocarcinoma the frog's tumor rarely metastasizes, only 1 instance having been found in over 200 cases studied.

In the majority of the tumors there are present prominent acidophilic intranuclear inclusions having the same general character as the inclusions of herpes, varicella and certain other virus diseases. The inclusions have been observed only in the epithelial cells of the tumor; they do not occur in the normal renal cells or in the cells of other organs. It seems probable that the nuclear changes represent the activity of a filtrable virus, though it is not yet certain whether such a virus has a causal relation to the new growths.

Experiments in transmission of the tumors are likewise as yet indecisive. Material from 24 tumors has been inoculated by various routes into a total of 478 frogs. In the majority of the cases the inoculated cellular material (a cell suspension or small fragments of tumor) was absorbed without leading to local new growth. In a relatively small number of cases some evidence of local new growth was obtained, such as a moderate degree of enlargement of the fragments, in which microscopic examination showed mitotic figures. Fragments of this kind were found for as long as one hundred days after implantation.

While transplantation of tumors has been largely unsuccessful so far as local growth is concerned, a number of the inoculated frogs have acquired renal tumors. Indeed the most massive tumors observed have occurred in previously inoculated animals. If the neoplastic disease is caused by a virus it is to be expected that its activity under experimental conditions will be manifest in that tissue in which the lesions occur spontaneously. The relatively more frequent finding of renal tumors in the inoculated series seems therefore in harmony with the present belief adopted as a working hypothesis, that a virus is the causal agent of the tumors.

Further support may or may not be obtained when the still surviving members of the inoculated series are examined.

NEW YORK PATHOLOGICAL SOCIETY

Regular Meeting, Feb. 22, 1934

WILLIAM C. VON GLAHN, *President*

HEMORRHAGIC DESTRUCTION OF THE OCULOMOTOR NERVE. ALFRED PLAUT.

The patient was a man 65 years old, who presumably had always been in good health. For one year or more ptosis of the right eyelid had been present. Since the patient had a cataract in that eye not much attention was paid to the ptosis. Four weeks before admission to the hospital severe headaches, mostly in the region of the ophthalmic branch of the right trigeminus nerve, set in. Occasionally there were nausea and vomiting. In the hospital the patient's blood pressure was found to be 160 systolic and 90 diastolic, and the clinical symptoms led to a diagnosis of ruptured aneurysm of the circle of Willis. Four days before death he suddenly lost consciousness; stupor and rigidity developed. The right oculomotor nerve was completely paralyzed. The spinal fluid contained fresh blood and showed xanthochromia at the same time. It had a pressure of 320 mm. of water.

At autopsy a subarachnoid hemorrhage, not very large, was found at the base of the brain. In the region where the aneurysm had been suspected by the neurologists an aneurysm-like, bluish sac the size of a large pea was found. At first glance it was considered to be an aneurysm of the posterior branch of the circulus arteriosus. After removal of the clotted material, however, the basal arteries were found completely intact, not even sclerotic. The bloody mass was the proximal stump of the severed right oculomotor nerve. During the removal of the brain no attention was paid to the distal portion of the oculomotor nerve. The first portion of the nerve was not hemorrhagic, the hemorrhage beginning gradually. The tip of the stump was extremely thin and ruptured during dissection. Microscopically the nerve tissue could be demonstrated even at the tip of the hemorrhagic stump. In the proximal portion of the nerve mild inflammatory changes were seen. Otherwise the brain was not remarkable except for moderate chronic internal hydrocephalus.

The unusual localization of the hemorrhage and the even more unusual self-amputation of the nerve cannot be satisfactorily explained. Hemorrhage in the oculomotor nerve has been described; for instance, in tuberculous meningitis. In one of the two cases described by M. Saenger in 1880 the hemorrhage in the oculomotor nerve was the only hemorrhage found in the brain. Another similarity between that case and this one was the change in the shape of the nerve, the cross-section becoming angular instead of round.

SUDDEN DEATH DURING LABOR. ALFRED PLAUT.

An obese, otherwise healthy, 25 year old Austrian Jewish primipara entered the hospital in the morning, the cervix partly dilated. Five hours later the cervix was nearly fully dilated and everything seemed normal, when she suddenly was taken with cyanosis, gasping and frothing at the mouth, and died within twenty minutes without convulsions. At autopsy the major portion of the pons was found occupied by hemorrhage, which had broken into the ventricles. Gross and microscopic examination of the blood vessels of the brain revealed no abnormality. The microscopic picture of the liver was normal; the kidneys showed a moderate degree of parenchymatous and hyaline change in the tubular epithelium and slight thickening of the walls of the glomerular capillaries. The antepartum course of the patient had been perfectly normal. In the last few months of her pregnancy her systolic blood pressure had risen from 108 to 125 mm. of mercury without a rise in the diastolic pressure (68). In December 1933 she had swelling of the feet, but her urine at that time was normal. A catheterized specimen taken at the onset of her fatal attack contained much albumin and occasional hyaline and granular casts.

In an attempt to find the explanation of this death, the following facts appear. The woman was very obese. Her liver was twice the normal weight (2,250 Gm.). It measured 30 by 21 by 8.5 cm. The spleen was also about twice the normal weight (330 Gm., measuring 15.5 by 9.5 by 5 cm.). In the absence of anomalies of tissue, the size of these organs must be taken as indicating a splanchnomegaly. On microscopic examination of the liver, unusually large nerve structures were noted in the surroundings of the large arterial branches. In the anterior lobe of the hypophysis a nerve structure 0.2 by 0.125 mm. was found. Such a finding is extremely unusual. Normally the hypophysis contains only very fine nerve fibrils which need special methods for demonstration. In many thousands of slides from the hypophysis I have never seen any nerve structure in the anterior lobe. The anterior lobe contained a rather large adenoma composed of pregnancy cells. In the center of the adenoma there was a hemorrhage, at the edge of which organization was seen. Thus this hemorrhage must have been older than the fatal pontile hemorrhage. The shape and staining characteristics of the hypophyseal cells outside the adenoma were very irregular.

Thus it seems that this hemorrhage occurred in a patient with multiple constitutional abnormalities, namely, abnormal nerve structures, splanchnomegaly and obesity. In addition, there must have been a renal disturbance, as indicated by the findings in the urine. Spontaneous hemorrhage of the brain in a really normal person during labor probably never occurs.

ALLERGIC INFLAMMATION OF THE LUNGS. B. M. FRIED (by invitation).

The report is based on experimental observations. Rabbits were sensitized by repeated intraperitoneal injections of horse serum. While some animals were sensitized with 20 cc. of horse serum, others required 40 cc. and more. The shocking injection of 1 cc. of serum was given intratracheally about one week after the last intraperitoneal injection. The animals were killed at intervals of from one hour to several weeks after the shocking injection. Studies were made of sections cut through the entire thickness of the lungs.

On gross examination areas of consolidation and discoloration were noticed in the lungs from animals that were killed in from twelve to fifteen hours after the intratracheal shocking injection, these areas being usually confined to the base or to the paravertebral region of the lung. Within twenty-four hours after the shocking injection about 60 per cent of the animals showed an entire lobe or a whole lung to be firm, with wide hemorrhagic areas scattered through the consolidated organ.

Under the microscope, too, changes were as a rule confined to one lung, involving the interstitial and the parenchymatous elements. Granulocytes and serum flooded the septal capillaries and the alveoli, leading to their immense distention shortly after the intratracheal injection.

This stage was succeeded by another in which the intra-alveolar exudate was composed of macrophages and eosinophils. Fibrin made its appearance within a few hours after the shocking injection.

There occurred profound changes in the vessels, such as disintegration of the vascular wall, which was infiltrated with round cells. The presence of fibrin in the wall, in the lumen and also in the edematous perivascular spaces was typical of the lesion. The vessels were surrounded by collars of "monocytoid" cells. The usually "quiescent" vascular endothelium showed morphologic changes and detached itself from the wall as single cells and en bloc. In many instances there occurred complete occlusion of vessels, with thrombus formation followed by infarctions.

In brief, the studies have revealed two points of particular interest: (1) a type of pulmonary inflammation that resembled genuine or lobar pneumonia; (2) vascular changes that looked like those observed in rheumatic fever and in periarteritis nodosa. It is remarkable that lesions of such grave nature can be induced with sterile horse serum without the intervention of pathogenic micro-organisms.

DISCUSSION

ALFRED PLAUT: Dr. Fried has mentioned the similarity of the vascular lesions to those seen in rheumatic fever and periarteritis nodosa. I must admit that I do not see that similarity. I see a simple inflammation of the blood vessels, and I wonder if other slides not depicted here really do show similarity between the allergic lesions in these lungs and the lesions found in periarteritis nodosa and rheumatic fever.

DAVID P. SEECOF: I should like to ask a few questions. How were the intratracheal injections made? Was a tracheotomy done, or was the injection made past the glottis? Does varying the dose, the amount injected into the trachea, cause any change in the reaction? In other words, was the reaction influenced by the dosage, and, if larger doses were given, were more lobes involved? Finally, how were the smaller bronchioles in the diseased lungs?

IRVING GRAEF: Were the changes confined to the consolidated lung, or were any also seen in the other lung or other organs? Also has Dr. Fried tried any species other than rabbits?

SYLVAN E. MOOLTEN: Can Dr. Fried distinguish either in degree or in kind between the inflammatory lesions he points out as allergic pneumonia and the simple aspirational reaction produced by foreign serum alone without previous sensitization or by extravasated blood? Did he find edema and fibrin in these alveoli as another evidence of an inflammatory reaction?

WILLIAM C. VON GLAHN: I should like to know whether there was fibrin in the walls of the vessels and what changes were found in the elastic tissue of the vessels.

B. M. FRIED: In answer to Dr. Plaut's question: I do believe the changes which I found resemble those seen in periarteritis nodosa and rheumatic fever. I should not say that it was a 100 per cent resemblance, but there were definite similarities between the condition which I observed in these lungs and the changes which I have seen in periarteritis nodosa and in some cases of rheumatic fever.

The second question concerned the method of injection. It was performed without a tracheotomy. The animal was placed on its back and fastened on the table; an incision was made in the skin, the muscles were separated, a sound was brought underneath the trachea and a fine needle was inserted into the trachea and the fluid pushed into the lung. It reached the finer bronchioles and the alveoli, without a doubt.

As to the influence of the dose on the reaction: I said before, serum is not an indifferent substance when injected into an animal's lung. A dose of 2 or 3 cc. produces a very definite reaction in the lung which will not subside for months, just as when one injects iodized poppy-seed oil 40 per cent or any oil it is slowly absorbed and remains for months in the lung in nodules, ultimately leading to secondary changes in the bronchi. Small amounts of serum were given in these experiments, and if the animal was properly sensitized these produced an effect. It was never necessary to inject more than 0.5 or 1 cc. I tried larger doses on normal animals, and found that with an amount of serum greater than 1 cc. the changes were permanent and grave. In these cases both lungs were involved, and the reaction was entirely different from that in these sections from allergic animals.

There was a question about the smaller bronchioles. In the early stage the reaction was not confined to the bronchioles. At a later date secondary changes in these structures occasionally occurred. Proliferation of the bronchial lining was noted, with possibly metaplastic changes.

In reply to Dr. Moolten: When a small amount of horse serum was given intratracheally there was no hemorrhage in the lungs. In these cases, the hemorrhage observed was the result of the vascular changes and of infarction.

There was considerable edema, sometimes leading to a marked distention of the alveoli.

In regard to changes in the other lung, there were none.

There were some changes in the liver and very slight changes in the heart. I was trying to be very cautious in the interpretation of my findings, and I did not want to go into details of the other organs. I therefore confined myself to the observations in the lungs.

In animals other than rabbits, such as guinea-pigs or rats, the induction of a local allergic reaction of the lung was a difficult matter. A study along this line is in progress.

Fibrin was present not only in the wall of the vessel but in the lumen and in the perivascular spaces. It is interesting to note that fibrin can be found in and around the walls of the vessels in the very early stages of the disease. I spoke of the fibrinoid reaction; actually shreds of fibrin could be seen in the wall of the vessel, in the lumen and in the perivascular spaces. The elastic tissue of the vessels was gravely injured.

DERMATOMYOSITIS: A REPORT OF TWO CASES. SIGMUND WILENS and ABNER WOLF (by invitation).

Two cases of dermatomyositis with the observations at autopsy are presented. One case was that of a man 53 years old, whose illness began three months before admission to the hospital with a dermatitis involving the skin of the upper extremities and face. Shortly thereafter he had weakness of the arms and legs. This was progressive and was followed by difficulty in swallowing and speech. On admission, he appeared chronically ill, showed extreme muscular weakness with considerable atrophy involving all the muscle groups, and had a dry, scaling, pruritic rash involving the face, chest and extremities. There was dysphagia. Mild fever was present; the white blood cell count was 24,000 with 85 per cent polymorphonuclears and 1 per cent eosinophils. The day following admission the patient, after finishing his lunch, suddenly became cyanotic, lapsed into stupor and died. At autopsy an extensive rash was noted over both forearms, upper arms and shoulders. The skin in these areas was scaly and roughened and slightly injected. It felt firm and was fixed to the underlying tissues. There was no pitting edema. All the skeletal muscles were pale, being light grayish red. They seemed to be normal in consistency.

The second case was that of a woman 47 years old, whose initial symptom was a dermatitis which developed eight months before admission to the hospital and involved the upper extremities. It was described as a red, scaling eruption. Three months later the dermatitis began to clear up, but eight weeks before admission difficulty in swallowing and speaking developed. Weakness in the legs and back soon appeared. On admission she appeared chronically ill and showed evidence of a loss in weight. Her speech was unintelligible, accompanied by great effort and followed by marked fatigue and dyspnea. The cutaneous eruption had entirely cleared save for some residual thickening. She showed increasing dyspnea and dysphagia and finally died. The clinical diagnosis was not definitely established, but the condition was thought to be bulbar paralysis terminating in poliomyelitis. At autopsy there were found slight scaling and thickening of the skin of the neck, hands, forearms, elbows and soles. There was no evidence of edema. The temporal, pectoralis minor and intercostal muscles were very pale, being grayish pink. The psoas major muscle, the right rectus femoris and the muscles of the back were also paler than normal, but the remainder of the skeletal muscles examined appeared grossly to be normal.

The microscopic findings in both cases were typical of dermatomyositis. No lesions were found in the central or the peripheral nervous system in either.

The pathology of the disease is as follows: The skin shows flattening of the papillae, marked increase of fibrous tissue in the cutis, edema, and mild round cell accumulations about the vessels and sweat glands. The muscles show loss of striations, fragmentation of fibrillae, hyaline or waxy degeneration, vacuolation, ruptured fibers, marked irregularity in the size and increase in the number of muscle and sarcolemma nuclei, blebbing of the sarcolemma sheath, perivascular

round cell infiltration, thickening and edema of the perimysium and endomysium and regenerative phenomena. In the more chronic cases there is a replacement fibrosis.

In the second of the cases, the creatine content of many of the affected muscles was studied. It was found to be definitely lowered, and there was a definite parallelism between the degree of involvement of a given muscle and the diminution of its creatine content. This corresponds to the findings of Steinitz and Steinfeld in the only other case of dermatomyositis in which such determinations have been made.

The etiology of the disease is unknown. Many different causative agents have been suggested. Unverricht suggested a gregarine; Langsteiner, a streptococcus; Bauer, a staphylococcus; Martinotti, a micrococcus, and others, different organisms. None of these organisms has been consistently found in the disease. Strümpell called attention to the occurrence of tuberculosis in some of the cases and thought there was a possible relationship. Grumke reported a case with a typical clinical syndrome in which the lesions were obviously tuberculous. The disease has been observed following infection of the upper respiratory tract, acute rheumatic fever, some of the acute infectious diseases of childhood and gastro-intestinal intoxications. It is possible that more than one agent may produce this condition or be predisposing factors. It is interesting that in our cases foci of infection were present: in the first case, a periappendical abscess; in the second, a tonsillar abscess. The type of onset, the fever, the angina, the frequently enlarged spleen and the type of the inflammatory changes in the muscle suggest the presence of an infectious process. Degenerative changes with secondary inflammatory phenomena in the skin and muscles due to toxins from some other primary condition form another possibility. Lesions produced in guinea-pigs and rabbits by Pappenheimer and Goettsch by special diets show some of the features of the muscular lesions of dermatomyositis. No definite evidence of improper nutrition has been encountered in the known cases of this disease, however.

DISCUSSION

PAUL KLEMPERER: In one of the two cases of dermatomyositis which I have seen, I observed arterial necrosis in some of the muscles, an observation which had already been made by Fahr in one of the cases which he reported. The presentation here is so detailed that it seems superfluous to ask whether any other changes were found. I presume not, otherwise they would have been mentioned, but I want to record this observation.

There is one question I want to ask: Was eosinophilia present during life, a finding which seems to be rather frequent in the cases reported? The most peculiar and characteristic feature of this disease is its unusual localization in the skin and musculature and occasionally in nerves, as mentioned, and it might be apropos to mention another case of myositis that I have seen in which the difference was that streptococci were found in great numbers in the musculature. This concerned a child who suffered with severe muscle pain for six days and died. At autopsy a large, septic spleen was found. Cultivation of this gave hemolytic streptococci in pure culture. All the muscles that were involved showed severe inflammation and necrosis, with an extremely large number of streptococci. The case may be considered as one of streptococcic septicemia with an unusual localization in the musculature. No other organ was affected. In some way this might throw light on the possible selective localization of toxins, Dr. Wilens having mentioned the infectious origin in his cases and in most of the cases cited in the literature of dermatomyositis.

ARTHUR SCHIFRIN: Was there any evidence of nephritis?

ROBERT O. FISHER: Does the disease occur without the cutaneous lesions?

ABNER WOLF: In answer to Dr. Klemperer's question: Neither case evidenced involvement of the arterial walls. Within the last week we saw a third

case in which there was marked arteritis in addition to the other changes which we noted. In neither case was an eosinophilia observed.

In reply to Dr. Schifrin's question: We did not observe any definite changes in the kidneys in either of the cases.

In answer to Dr. Fisher: The disease can occur without evident changes in the skin. The changes in the skin may be fleeting and may not be impressive enough to be noted in the clinical picture, although in the majority of cases described in the literature there have been cutaneous lesions. As Dr. Wilens observed, these skin changes may have a variable relationship to the appearance of the muscle symptoms; they may come before the muscle symptoms or they may appear very late in the disease.

GIANT CELL LEUKEMIA. PAUL KLEMPERER.

A case of chronic myeloid leukemia in which there were no unusual clinical, hematologic or gross anatomic features but in which the histologic examination revealed an excessive number of megakaryocytes within the spleen and lymph nodes is described. The origin of the megakaryocytes could be traced to hematic stem cells (hemocytoblasts), but occasionally the fixed reticulum cells of the spleen and lymph nodes also showed evidence of transformation into giant cells. The endothelium of the splenic sinus, however, showed no evidence of proliferation. Conspicuous accumulations of megakaryocytes and erythroblasts were found in the peripheries of anemic infarcts in the spleen.

DISCUSSION

MAURICE N. RICHTER: Cases of the type that Dr. Klemperer has reported are very unusual, and I think they are even more unusual than he has indicated. I have seen a somewhat similar one recently which I think corresponded a little more to the type usually described in the literature. Many cases in which the megakaryocytes have been unusually common have been cases of aleukemic myelosis. Furthermore, a number of the cases have been associated with osteosclerosis, and in the one which I studied osteosclerosis was present in the sternum, femur, ribs and vertebral marrow. The sclerosis was present to such an extent that the remaining marrow could not be recognized as that from a patient with myeloid leukemia, and megakaryocytes in particular were practically absent from the bone marrow, so that one can hardly consider them as embolic from that source. Cases in which osteosclerosis, a low white blood cell count and numerous megakaryocytes were present have been observed a number of times, so often that it seems to me there must be some significance in the association of these three rather unusual features.

ALFRED PLAUT: In January I had an opportunity of observing something similar in a patient who had had polycythemia. A year before death this patient had 16 liters of blood. Then the polycythemia disappeared, and the patient died with old abscesses of the liver and many other lesions. The first thing that drew attention to the fact that the patient had an aleukemic leukemia was the large number of megakaryocytes in the lymph nodes, spleen and liver. This was not considered to indicate a special disease, but to be just an observation of aleukemic leukemia with a large number of megakaryocytes, and there was no hesitation in assuming that the megakaryocytes had originated in the spleen and in the lymph nodes. As to the question of origin, one might cite the simple fact that certain animals have megakaryocytes normally in the spleen, and probably nobody would think of them as of embolic origin.

SEATON SAILER: I should like to ask if there is any explanation for the reduction in the number of platelets, in view of the proliferation of the megakaryocytes and the fragmentation of some of them.

PAUL KLEMPERER: The fact that in osteosclerotic leukemia the megakaryocytes in the internal organs are increased in number was also borne out by one of the other cases in my series. There was also leukopenia.

Regarding Dr. Sailer's question as to the explanation for the low platelet count in this instance, I can refer to other cases in which the same observation was made. It is peculiar that in spite of the marked proliferation of megakaryocytes and the marked fragmentation there were not more megakaryocytes in the circulating blood. There is one factor that has to be considered, namely, that the presence of megakaryocytes and the separation of platelets within the spleen need not lead to an increase in the number of platelets in the general circulation, for they might be destroyed within the portal system and then might be filtered out in the lung. Another explanation has been given, that the megakaryocytes do not properly form platelets. In the case which I have described this was not suggested, for one could see the formation of platelets from the megakaryocytes within the tissues.

CHICAGO PATHOLOGICAL SOCIETY

Regular Monthly Meeting, Feb. 12, 1934

E. H. HATTON, *President, in the Chair*

INFECTIOUS MONONUCLEOSIS. I. DAVIDSOHN.

The demonstration by Paul and Bunnel of an increase in heterophilic antibodies in the blood of patients with infectious mononucleosis is an important contribution to knowledge of the disease. This observation has been confirmed repeatedly. My report is presented to emphasize the value of an examination of the serum for heterophilic antibodies.

A 19 year old white boy, a patient of Dr. Richard Gordon, was admitted to the Mount Sinai Hospital, Sept. 28, 1933, with pain in the abdomen and in the right axilla which had lasted for five days, and a swelling in the right axilla of three days' duration. At first the pain in the abdomen was generalized; then it localized in the lower portions. He had a feeling of distention but no nausea or vomiting. Constipation of three days' duration was relieved by a cathartic. His past and family histories are not important. Physical examination revealed that the cervical, left axillary, and both inguinal lymph nodes were enlarged. In the right axilla was a mass about the size of a walnut. The nodes were tender, the mass in the right axilla more than the others. The firm, tender spleen extended about 1 fingerbreadth below the costal margin. The liver was enlarged and tender. There was some sensitiveness in the right lower quadrant of the abdomen. The temperature on admission was 100.8 F.; the pulse rate, 88; the respiratory rate, 24. Acute appendicitis was considered. Examination of the blood on the following day revealed a leukocytosis of 13,750 in which 2 per cent were band forms. 12 per cent segmented neutrophils, 1 per cent eosinophils and 1 per cent basophils. The remaining 84 per cent were mononuclear cells, of which 63 per cent were lymphocytes, 1 per cent plasma cells, 6 per cent monocytes and 14 per cent abnormal lymphocytes. The conditions in the blood and the clinical symptoms suggested infectious mononucleosis. The test for heterophilic antibodies in the serum demonstrated a high titer (1:5,120) of agglutinins for sheep red cells. (The technic of the test will be presented in detail in an extended report.) Sections of a lymph node from the groin showed hyperplasia of the endothelial cells. The tissue changes were similar to those described in previous reports. The patient left the hospital on the third day after admission but remained under observation. The spleen was not palpable on the eighteenth day after the onset of symptoms; the lymph nodes were not tender, but their size decreased very slowly, and some were distinctly enlarged after four and a half months. Abnormal lymphocytes were seen until three weeks after the onset, but the mononucleosis (51 per cent) was present after four and a half months.

COALESCED GLANDULAR CARCINOMA AND LYMPHOSARCOMA OF THE COLON.

C. S. HAGERTY.

Malignant tumors of both carcinoma and sarcoma are rare. Glaessen and Mathias (*Beitr. z. path. Anat. u. z. allg. Path.* **123**:584, 1921) compiled seventy-one reports of such tumors and Jaffé (*Surg., Gynec. & Obst.* **37**:472, 1923) thirty-two. Ehrlich and Apolant (Ewing, J.: Neoplastic Diseases, ed. 3, Philadelphia, W. B. Saunders Company, 1928, p. 1018) obtained a tumor with epiblastic and mesoblastic tissues by transplanting carcinoma through several generations of mice. In man, tumors of sarcoma and carcinoma occur with greatest frequency in the uterus, ovary, thyroid gland and digestive tract. Schubach (*Ztschr. f. Krebsforsch.* **33**:126, 1931) described a gastric tumor of undifferentiated carcinoma and lymphosarcoma. A tumor of the colon, similar in structure to that described by Schubach but with more clearly differentiated tissue components, is now reported.

A white woman, aged 59, a patient of Dr. L. E. Schmidt, entered St. Luke's Hospital, June 20, 1933, because of pain in the left kidney of eight months' duration. She had had pulmonary tuberculosis in 1925; in 1931, the uterus was removed because of a glandular carcinoma of the fundus. A parent and a sister had died of carcioma. A pyelogram of the left kidney demonstrated a nearby mass which by operation was determined to be a tumor of the descending colon. The excision of the growth was done by Dr. C. G. Shearon. The patient did not survive the operation.

The colonic segment was 12 cm. long and 9 cm. in circumference. In the center of the lining was an annular ulcerated growth with rounded edges, 3.5 cm. in diameter, projecting 4 cm. above the mucosa. The cut surfaces were opaque gray-white. The lining surface covering the tumor was uneven; in the ulcerated center was a stellate perforation 3 mm. in diameter. The mucosa about the tumor was unchanged.

In the histologic preparations large regions of necrosis were found. There were two types of tissue, varying in amount, in the places examined. The first, mainly along the lining edge, was glandular carcinoma in tubules and papillae. The stroma consisted of fibroblastic tissues with inflammatory exudates of the second variety of tumor tissue. This had a delicate fibrillar stroma with the polymorphous cells and grouping seen in the Kundrat lymphosarcoma.

The postmortem examination, two hours after death, showed: surgical anastomosis of the colon below the splenic flexure (resected neoplasm); edema of both lungs; chronic fibrous myocarditis, and chronic fibrocalcareous tuberculosis of the lungs. The examination was restricted to the thorax and abdomen, in which careful search failed to reveal metastases in the viscera.

Tumors of malignant epiblastic and mesoblastic tissues, as a rule, are designated carcinosarcoma or sarcocarcinoma, depending on the type of tissue predominant. Gotting (*Frankfurt. Ztschr. f. Path.* **41**:107, 1931) stated that a carcinosarcoma may arise in one of the following ways: (1) the stroma of a carcinoma may become a sarcoma; (2) a carcinoma and a sarcoma may develop separately and as a result of rapid growth show an intermingling of their cells, or (3) carcinoma and sarcoma may develop from a matrix having epiblastic and mesoblastic potentialities. A fourth, but now discredited, possibility is the transformation of a carcinoma into a sarcoma, or vice versa.

The carcinosarcoma produced experimentally in animals is thought by Coenen and Simmonds to demonstrate that the stroma of a carcinoma has developed into a sarcoma. They refer to this growth as a mutation tumor, to designate a change in the quality of the tissue. The implanted tissue is usually carcinoma, and after transplantation through several generations of animals the pure carcinoma may change to carcinoma and sarcoma. The stimulating factor of the carcinoma, it is thought, is responsible for this change. The rarity of carcinosarcoma, however, seems to preclude this possibility.

Two malignant tumors may develop in the same organ independently. Because of their close proximity and rapid growth the two types of malignant tissue intermingle, and the resultant tissue is that of a carcinosarcoma. (collision tumor). The tumor elements are related to each other as stroma is to parenchyma. Tumors of this type are usually found in the uterus and the ovaries.

The tumor of the colon described is regarded as a glandular carcinoma and a lymphosarcoma developing independently, though possibly due to a common stimulus. The close proximity of the two tumors resulted in fusion. If named according to the possibilities of origin, the tumor is properly called a collision carcinolymphosarcoma. Schubach interpreted the tumor in his patient similarly and designated the growth a collision carcinolymphosarcoma of the stomach.

Apparently the tissues of my patient had some inherent tendency to become malignant, since a carcinoma of the uterus and a combined glandular carcinoma and lymphosarcoma of the colon developed within two years.

DISCUSSION

EMIL RIES: Years ago a search was made for sarcoma of the endometrium in the presence of carcinoma of the uterus. No attention is given now to this possibility.

P. DELANEY: Malignant tumor of the thyroid gland with spindle-shaped cells has been considered a mixed tumor, but I doubt that it is, because epithelium can behave very strangely in tumor tissues.

E. F. HIRSCH: A malignant growth of the thyroid gland (*Am. J. Cancer* **15**:55, 1931) had long spindle-shaped cells with the cross-striations of skeletal muscle. Even remote metastases had cells with these characteristics.

PURIFICATION OF THE VIRUS OF POLIOMYELITIS. JAMES A. HARRISON.

The virus of experimental poliomyelitis has been treated in a variety of ways designed to effect purification. My associates and I have had occasion to use the method of Clifton, Schultz and Gebhardt, employing treatment with ether, and the method of Sabin, using aluminum hydroxide adsorption, in the preparation of virus for serologic studies. A combination of these treatments has enabled us to obtain from emulsions of the cord tissue of infected monkeys water-clear, colorless virus preparations which have been uniformly infectious in a large number of tests. The virus present in concentrates of such preparations (produced by boiling them in vacuo) survives at least four hours of tryptic digestion and subsequent dialysis against distilled water for twenty-four hours. These final virus preparations have not been anticomplementary in comparative 40 per cent suspensions, whereas crude suspensions of the virus-containing cord tissue are anticomplementary in 1 per cent suspensions.

DISCUSSION

W. J. NUNGESTER: There is a possibility of loss of virus through these manipulations. The loss probably would be less with desiccation in vacuo than in the presence of oxygen.

LEIOMYOSARCOMA OF THE ADULT KIDNEY. P. A. DELANEY.

Oct. 15, 1933, a white man, aged 51, had an acute pain in the region of the left ilium radiating to the left lumbar region. A tender, hard mass, about the size of a large grapefruit, freely movable, thought to be the left kidney, was palpable in the left side of the upper part of the abdomen. He had had three intermittent attacks of hematuria during fourteen months; during the past six months he had lost 40 pounds (18.1 Kg.) in weight and had been lethargic, and for four months he had had no appetite. October 16, the patient entered the Englewood Hospital. Roentgen examination demonstrated a markedly enlarged left kidney, which was removed, October 21. It weighed 480 Gm. The outer surface was

nodular and hemorrhagic. Friable tissues perforated the capsule laterally, into the pelvis and hilus, and extended along the renal vein. The capsule stripped readily. A frontal section revealed friable, hemorrhagic tumor tissue and small masses of renal cortex and medulla. There were tumor thrombi in the main portion and in the large branches of the renal vein. Microscopically, no part of the kidney was unchanged. The cortex and medulla were replaced by a tissue morphologically and tinctorially spindle-shaped smooth muscle cells with intracellular fibrillae. Considerable tumor tissue was necrotic. Small masses of renal parenchyma, not invaded by the tumor, had glomeruli and tubules distorted by pressure. There were many casts in the dilated tubules. Portions of the renal pelvis and of the upper part of the ureter were invaded by tumor tissues. Large and small veins were completely occluded by tumor thrombi. Myoblasts infiltrated the fat tissues of the renal hilus.

Regular Monthly Meeting, March 12, 1934

E. H. HATTON, *President, in the Chair*

OSTEOMALACIA IN A MAN. FRANCIS D. GUNN and WALTER H. NADLER.

A clinical description of this case was published in 1917 by Elliott and Nadler (*Tr. Chicago Soc. Int. Med.* **1-2**:56, 1917). Evidences of the disease appeared when the patient was about 19 years of age and continued for twenty-one years. During eleven years of observation no significant findings other than the changes in the bones were made. There was no history of dietary deficiency. Castration apparently did not alter the course of the disease. Pathologic fractures occurred late in the disease, and death occurred when the patient was 40 years of age, following an acute infection of the upper respiratory tract and cardiac decompensation.

Necropsy revealed fatty degeneration of the myocardium, chronic passive hyperemia of the liver, parenchymatous degeneration of the kidneys and generalized decalcification and rarefaction of the bones without the presence of cysts or brown tumors.

The glands of internal secretion were normal grossly and microscopically with the exception of the hypophysis and parathyroid glands. The hypophysis showed slight hypertrophy (0.95 Gm.), but without selective hyperplasia of any one type of cell. There were only two parathyroid glands; each was definitely enlarged, but microscopically the only deviation from normal was a diminished number of fat cells and mild simple hyperplasia of the parenchyma. The renal stroma contained numerous small calcareous deposits.

The hypertrophy and hyperplasia of the parathyroid glands are interpreted as compensatory, due to increased physiologic activity.

The report will be published in full in the *Archives of Internal Medicine.*

METEOROLOGICAL FACTORS IN THE EPIDEMIC OF POLIOMYELITIS. WILLIAM F. PETERSEN.

Evidence was first presented concerning the association of a severe polar infall with the precipitation of a syphilitic poliomyelitis. The city records indicate precipitation of poliomyelitis at the same time. The poliomyelitic records of Detroit, Windsor, Ont., Toronto, Chicago, Milwaukee, Duluth, Minn., St. Paul, Kansas City, Mo., and other adjacent cities indicate the frequent precipitation of acute poliomyelitic episodes with the passage of polar fronts. As a result coincident cases are evident in remote cities at the same time.

Attention was called to the fact that a pressor episode (with periods of relative anoxemia in vessels of the spinal cord) may so condition definite regions of the central nervous system that localization of a virus may result in seemingly selective foci.

"Brenner Tumor" of the Ovary of Unusual Size. Marshall Davison and Benjamin H. Neiman.

An ovarian tumor weighing 15 pounds (6.8 Kg.) was found at operation in a nulliparous Negress 45 years of age. Her menses had stopped two years previous to her entrance into the hospital. The tumor occupied the position of the left ovary. The remaining adnexae uteri had no gross changes.

Histologic preparations of the tumor contained groups of epithelial cells separated by a dense stroma of connective tissue. Some of the fibrils, especially about the epithelial cells, were hyalinized. Many of the cell masses were solid aggregates; others had clefts which formed small cysts filled with mucoid material.

Foci of Walthard cells may develop in one direction or another, depending on various influences, and form abnormal structures. If the foci of Walthard cells retain their indifferent character in the course of development, the solid Brenner tumor develops. If the differentiation of the cells tends primarily in the direction of cyst formation, the second type of Brenner tumor develops in which the cyst formation reaches such an extent that a cystoma appears, with an intramural Brenner nodule.

Since "Brenner tumor" is a misnomer from a historical point of view, and is of little value in describing the condition, the term "benign mucinous or pseudo-mucinous fibro-epithelioma," suggested by Plaut, seems to be more applicable.

DISCUSSION

J. I. Brewer: In two patients with these growths whom Dr. H. O. Jones and I have had under observation (*Am. J. Obst. & Gynec.* **25**:505, 1933) there were manifestations of hormonal activity.

Fibromyoma of the Ileum. I. Pilot and Sam Brock.

Benign tumor of the small bowel is comparatively rare and seldom recognized before operation. We report a case because of the complication of the tumor by infection. The literature on benign tumors of the ileum down to 1927 has been summarized by Clifton and Landry (*Boston M. & S. J.* **197**:8, 1927). Other reports on these tumors are by Key Oberg (*Acta chir. Scandinav.* **62**:261, 1927), Goldsmith (ibid. **62**:261, 1927), Boutreau-Roussel and Cadenat (*Bull. et mém. Soc. nat. de chir.* **53**:921, 1927), Sorkness (*Journal-Lancet* **48**:146, 1928), Steindl (*Wien. med. Wchnschr.* **79**:1256, 1929) and Marintschik (*Zentralbl. f. Chir.* **56**: 1362, 1929).

A white man, aged 50, a sheet-metal worker, entered the Edgewater Hospital, Dec. 18, 1930, with sharp, lancinating pain in the lower part of the abdomen, which began suddenly about thirty-six hours before. The patient said that he had had occasional similar attacks for about three months. He had had no chills or fever and had noticed no change in the character of his stools. His appetite had been poor, and he had lost about 10 pounds (4.5 Kg.) in weight; he was a small, thin man. The abdomen was moderately tender and rigid, especially over the suprapubic region. No masses were palpable. Under spinal anesthesia a right pararectus incision was made. The peritoneum contained a small amount of cloudy fluid with a foul odor. There was a diffuse peritonitis. The appendix was bound by adhesions. The pelvis contained a soft, boggy mass—a tumor attached to the ileum. It had prolapsed into the pelvis and was adherent to the rectum and sigmoid. On freeing the mass and the small bowel, the tumor ruptured, and a small amount of putrid material escaped. The tumor arose from the lateral surface of the bowel. It was soft and contained regions of fluctuation. As it was considered a malignant growth, it was resected, with 5 cm. of bowel extending proximally and distally.

The resected portion was 13 cm. long. At its free margin was a pedunculated mass, 7 cm. long and 6 cm. in diameter, that arose from the muscularis. The

pedicle was 3 cm. in diameter. A gray area of softening on the serosa extended into an abscess in the center, which was filled with foul green exudate. The remainder of the tumor was soft and grayish yellow. The mucosa of the intestine was smooth except for a small opening that led from the lumen into the abscess of the tumor. The exudate in the abscess contained many gram-negative bacilli and gram-positive cocci.

Microscopically the tumor showed interlacing bundles of smooth muscle cells and small amounts of fibrous tissue. Blood vessels were few.

The growth had several interesting features. The first clinical manifestation was an acute peritonitis, undoubtedly the result of a perforation of the abscess into the peritoneal cavity. The central abscess communicated with the intestinal lumen through a narrow fistula, with insufficient drainage, causing progressive softening and extension to the peritoneum. The tumor was outside the main plane of the intestinal wall and produced no obstructive symptoms.

DISCUSSION

PAUL CANNON: Recently, during postmortem examination of the body of a man, aged 45, I found in the jejunum a fleshy mass with an abscess. Histologically the tissues were like those of the tumor described by Dr. Pilot. There were secondary abscesses of the liver. Colon bacilli and streptococci were isolated from the infected tissues.

E. B. FINK: A girl, aged 6, had abdominal symptoms due to a fibroma protruding into the lumen of the ileum.

Book Reviews

Précis de microscopie: technique, expérimentation, diagnostic. By M. Langeron, Chef de laboratoire à la Faculté de Médecine de Paris, Directeur-adjoint à l'Ecole pratique des Hautes-Etudes, Secrétaire général des Annales de parasitologie humaine et comparée. Fifth edition, entirely rewritten. Price, 100 francs. Pp. 1,205, with 365 figures. Paris: Masson & Cie, 1934.

The fact that the book is in its fifth edition since it was first published in 1913 proves that it fills a need in the French medical literature. The reason for that success becomes apparent even after a casual study of its contents. The physics of the microscope, its various applications and its proper care are presented in 273 pages. This chapter is up to date and includes all recent developments in this rapidly growing technical field. A discussion of the "ultropaque" lens, which was only recently put on the market by the optical firm of Leitz, may serve as an example of the completeness of the presentation. The chapter on microphotography has some good practical suggestions. The second part, consisting of 381 pages, deals with histologic technic in its broad meaning. The beginner is introduced in a clear and effortless manner into all phases of histologic technic, but even the most expert and experienced worker will find a veritable mine of facts. Discussions of the various applications of carmine (6 pages), of hematoxylin (14 pages) and of impregnation with metals (30 pages) are picked at random as a few representative examples of Langeron's excellent presentation. Many valuable suggestions will be particularly appreciated by those who have made histologic preparations and still more so by those who have been frequently baffled by the imperfections in the slides prepared for them by technicians. They will find on page 632, in addition to many references in the text, an instructive discussion of the common errors in histologic technic and of the ways to avoid them. Each procedure is preceded by a lucid presentation of the underlying theoretical background, so that the book is not merely a compilation of technical details. The evaluation of technical methods and their pros and cons are discussed frankly and objectively. The third part deals with the study of the Protozoa and the Metazoa. It includes brief chapters on the blood, cerebrospinal fluid, sputum, milk and urine. Medicolegal microscopy is discussed on 6 pages. Sixty-five pages are devoted to bacteriologic and mycologic technic. A presentation of essentials of botanical technic and tables of physical and chemical constants complete the contents. The index and bibliographic references are very complete.

The book can be well recommended primarily for those interested in histology and in clinical pathology.

Brucella Infections in Animals and Man. Methods of Laboratory Diagnosis. I. Forest Huddleson, Department of Bacteriology and Hygiene, Michigan State College. Price, $2.25. Pp. 125, with 24 illustrations. New York: The Commonwealth Fund, 1934.

This book emphasizes the common interests of the workers in human and veterinary aspects of Brucella infections. It is restricted almost entirely to a description of technical laboratory procedures for the diagnosis of Brucella infection. There are some brief references to interpretations and findings. The procedures which originated through the author's own work are presented clearly. An extensive bibliography is included. The book is a valuable technical guide; pathologists will be interested particularly in the rather short chapter on structural changes in Brucella infections.

Books Received

COLLECTED REPRINTS FROM THE LABORATORIES OF THE MOUNT SINAI HOSPITAL, NEW YORK. Louis Gross, M.D., Director, 1933.

URINARY ANALYSIS AND DIAGNOSIS BY MICROSCOPICAL AND CHEMICAL EXAMINATION. Louis Heitzmann, M.D., New York, Formerly Professor of Pathology and Bacteriology, Fordham University School of Medicine, New York. With a Chapter on the Determination of the Functional Efficiency of the Kidneys by Walter T. Dannreuther, M.D., F.A.C.S., Professor of Gynecology and Director of Department, New York Post-Graduate Medical School and Hospital, Columbia University. Sixth revised edition. Price, $5. Pp. 385, with 131 illustrations. Baltimore: William Wood & Company, 1934.

The first edition of this book was published in 1899. The present edition has been brought up to date, but the chemical tests described are such as "can be performed without the necessity of a completely equipped chemical laboratory, by the technician or the physician. . . ." A short new chapter on the hormone tests for pregnancy is introduced. The illustrations, all more or less diagrammatic and rather crude, appear to be the same as those in earlier editions.

BRUCELLOSIS: A PUBLIC HEALTH PROBLEM. Ward Giltner. Pp. 118. East Lansing: Michigan State College, 1934.

THE MEDICOLEGAL NECROPSY. A Symposium held at the Twelfth Annual Convention of the American Society of Clinical Pathologists at Milwaukee, June 9, 1933. Edited for the Society by Thomas B. Magath. Price, $2.50. Pp. 167. Baltimore: Williams & Wilkins Company, 1934.

The contents of the book are: introduction, Frederic E. Sondern; the medicolegal system of the United States, Oscar T. Schultz; the medicolegal necropsy, Charles Norris; performing the medicolegal necropsy, A. V. St. George; pathologic anatomy of death by drowning, Edward L. Miloslavich; toxicology in the medicolegal autopsy, Alexander O. Gettler; medical examiner's findings in deaths from shooting, stabbing, cutting and asphyxia, Harrison S. Martland; report on necropsies (reprinted from the ARCHIVES [**14**:701, 1932]) by joint committee representing the New York Academy of Medicine, the New York Pathological Society and the Metropolitan Funeral Directors' Association. These articles are reprinted from the January 1934 issue of the *American Journal of Clinical Pathology*.

REPORT OF THE LABORATORY AND MUSEUM OF COMPARATIVE PATHOLOGY OF THE ZOOLOGICAL SOCIETY OF PHILADELPHIA. Herbert Fox, M.D., Pathologist. Pp. 55. 1934.

CORRECTION

In the first line of the fourth paragraph of the abstract of the article by Dr. Raymond S. Rosedale, entitled "Congenital Heart Disease: Interventricular Septal Defect, Dextroposition of Aorta, and Dilatation of Pulmonary Artery," which appeared on page 721 of the May 1934 issue of the ARCHIVES OF PATHOLOGY, in the proceedings of the Buffalo Pathological Society, the word "not" should be eliminated, making the sentence read: "The normal equal division of the truncus and bulbus arteriosus had taken place, for the remainder of the aorta which is not concerned with the septum trunci was of the same caliber as the ascending portion."